Exhibit B

Report re: the Gynecare TVT™ Retropubic
Teresa Irwin, M.D., F.A.C.O.G., F.P.M.R.S

This report contains a summary of my qualifications, education, training, and experience, a complete statement of my opinions that I have formed to date, the basis for those opinions, and the information I considered in forming my opinions. All of my opinions are based on my education, training, clinical experience, the pertinent medical literature, discussions with colleagues and other materials I have reviewed. Materials that support my findings and opinions, including documents that I have reviewed, are identified either in this report or are listed in an attachment to this report.

During the previous four years, I have not testified as an expert witness at trial or by deposition. I am being compensated $300 per hour for my study and testimony in this case.

All of my opinions are held to a reasonable degree of medical and scientific certainty. If I receive additional information after signing this report but before trial, I may form additional or different opinions.

BACKGROUND

I attended the University of Texas El Paso, College of Nursing and Allied Health, graduating with a Bachelor of Science degree in Nursing in 1990. I attended medical school at University of Texas Health Science Center at Houston, earning my Medical Doctorate in 1996. I then did my internship and residency in Obstetrics & Gynecology at Baylor College of Medicine in Houston, Texas from 1996 to 2000.

I am Board Certified in Female Pelvic Medicine and Reconstructive Surgery, and by the American Board of Obstetrics and Gynecology. I am also a Fellow of the American College of Obstetrics and Gynecology. I am an active member of the American Urogynecologic Society (AUGS) and the American Medical Association (AMA). My curriculum vitae is attached to this report.

I have performed multiple types of urinary incontinence procedures including the following:

- Anterior colporrhaphy and Kelly plication
- Burch Retropubic Urethropexy
- Autologous Fascia Lata Pubovaginal Sling
- AMS Monarc™ Subfascial Hammock
- AMS MiniArc™ Single-Incision Sling System
- GMD Universal Urinary Incontinence Sling

- Ethicon GYNECARE TVT EXACT® Continence System
- Caldera Desara® sling system
- Boston Scientific Advantage Fit™ Transvaginal Mid-Urethral Sling System
- Boston Scientific Solyx™ Single-Incision Sling System
- Boston Scientific Urethral Bulking with Coaptite™ Injectable I
- Coloplast T-sling
- Coloplast Altis Single Incision Sling
- Coloplast Urethral Bulking with DurasphereEXP

UI: IMPACT ON HEALTH, EPIDEMIOLOGY, CLASSIFICATIONS, SURGICAL CANDIDATES

Urinary incontinence (UI), the involuntary leakage of urine, often remains undetected and under-treated. Approximately 44% of community-dwelling women seek care for urinary incontinence [***1****:Harris SS, Link CL, Tennstedt SL, Kusek JW, McKinlay JB. Care seeking and treatment for urinary incontinence in a diverse population. J Urol. 2007;177(2):680;* ***2****: Hannestad YS, Rortveit G, Hunskaar S. Scand J. Help-seeking and associated factors in female urinary incontinence. The Norwegian EPINCONT Study. Epidemiology of Incontinence in the County of Nord-Trøndelag. Prim Health Care. 2002 Jun;20(2):102-7;* ***3****: Morrill, et al. Seeking healthcare for pelvic floor disorders: a population-based study. Am J Obstet Gynecol. 2007 Jul;197(1):86.e1-6*]. Patients may be hesitant to initiate discussions about their incontinence and urinary symptoms due to embarrassment, lack of knowledge about treatment options, and/or fear of surgery.

IMPACT ON HEALTH

Urinary incontinence is not associated with increased mortality, but it can impact many other aspects of a patient's health.

- **Quality of life.** Urinary incontinence is associated with depression and anxiety, work impairment and social isolation [**4**: *Coyne et al. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study; BJU Int. 2008;101(11):1388*; ***5***: *Yip SK, Cardozo L. Psychological morbidity and female urinary incontinence. Best Pract Res Clin Obstet Gynaecol. 2007 Apr;21(2):321-9*); **6**: *Ratner et al, Maturitas. Sexual satisfaction in the elderly female population: A special focus on women with gynecologic pathology. 2011 Nov;70(3):210-5*; ***7***: *Coyne KS, et al. The burden of lower urinary tract symptoms: evaluating the effect of LUTS on health-related quality of life, anxiety and depression: EpiLUTS. BJU Int. 2009 Apr;103 Suppl 3:4-11*; [**8**: *Barber MD et al. Sexual function in women with urinary incontinence and pelvic organ prolapse. Continence Program for Women Research Group; Obstet Gynecol. 2002;99(2):281*]. Even nursing home residents experienced depression, anxiety and social isolation related to urinary incontinence [***9****: Dubeau CE, Simon SE, Morris JN. The effect of urinary incontinence on quality of life in older nursing home residents. J Am Geriatr Soc. 2006;54(9):1325;* ***10:*** *Cox A, Herschorn S, Lee L. Surgical management of female SUI: is there a gold standard? Nature reviews/ urology 2013; 10: 78-89*]. I have many examples where patients have an impaired QOL as a result of

UI. It can range from what one might consider a minor QOL, such as having to scope out every restroom at every place the patient goes to, to completely shutting herself up in her home to avoid the embarrassment of wetting her clothes or because of “smelling bad,” as if she was from a nursing home. One young patient told me her friends thought she was doing "drugs" because she was constantly going to the bathroom. One grandmother told me she stopped taking her grandchildren to the movies, because they would make "snide" remarks about her disrupting the movie, since she was getting up to go to the restroom every 30-45 minutes; and another had to leave her job because it was becoming disruptive to the workflow of the office. These are just a few examples of how a woman's life is impacted socially, emotionally and professionally.

- **Sexual dysfunction.** Urinary incontinence during intercourse, or coital incontinence (a form of stress urinary incontinence), can affect up to one-third of all incontinent individuals. Therefore, the fear and embarrassment of incontinence during sexual activity often leads to sexual dysfunction [***11**: Serati M, Salvatore S, Uccella S, Nappi RE, Bolis P. Female urinary incontinence during intercourse: a review on an understudied problem for women's sexuality. J Sex Med. 2009;6(1):40*].

- **Morbidity.** The moisture and irritation from the contact to urine, can lead to genital infections such as yeast and/or cellulitis (when bacteria spread through the skin into the deeper tissues). In addition, falls and fractures are more prevalent in those who have UI, especially in the elderly, vision impaired or those with nocturia [***12**: Brown JS, Vittinghoff E, Wyman JF, Stone KL, Nevitt MC, Ensrud KE, Grady D. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc. 2000;48(7):721*].

- **Increased caregiver burden**. There is an increased caregiver burden, especially for the elderly with UI. 6-10% of nursing home admissions in the United States are attributable to urinary incontinence [***13**: Morrison A, Levy R. Fraction of nursing home admissions attributable to urinary incontinence. Value Health. 2006;9(4):272*].

- **Economic burden**. Urinary incontinence imposes a significant financial burden on individuals, their families, and healthcare organizations. For individuals 65 years of age and older these costs are substantial, increasing from $8.2 billion (1984 dollars) to $16.4 billion (1993 dollars). Both of these cost-of-illness estimates, however, relied on data and factors that have changed over time. This study updates these cost estimates. The 1995 societal cost of incontinence for individuals aged 65 years and older was $26.3 billion, or $3565 per individual with urinary incontinence [***14:** Wagner, T, Teh-Wei, H. Economic Costs of Urinary Incontinence. Journal of Urology 1998;51:355-361*]. An estimated 17 million community dwelling adults in the United States had daily UI in the year 2000. Based upon a research article published in 2010, estimates of the total annual cost for urinary incontinence is approximately $32 billion; with SUI being highly prevalent, especially in women [***15:** Staack A, Rodriguez LV. Stem Cells for the Treat-*

ment of Urinary Incontinence. Curr Urol Rep (2011) 12:41–46].This number is probably underestimated, as in less than 1/3 of women with new UI were being treated by general practitioners. UI is often undetected and underreported by hospital and nursing personnel [***16*****:** *Levy PhD, R. and Muller, N. Economic Burden and new Choices in Pharmaceutical Treatment. Advances in Therapy: vol 23, No. r, July/ Aug 2006*].

EPIDEMIOLOGY

The prevalence of urinary incontinence is common in women, particularly in pregnancy. Estimates of prevalence vary depending on the population studied and the instruments used to assess severity. Based upon the Cochrane Collaboration review published in 2015, evaluating 81 trials that had a total of 12,113 women, urinary incontinence is a very common and debilitating problem. It affects about 50% of women at some point in their lives. Stress urinary incontinence (SUI) is a contributory or predominant cause in 30% to 80% of these women [***17***: *Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database of Systematic Reviews 2015, Issue 7: CD0063*]. In another study, using a validated questionnaire among women aged 25 to 84 years in a large United States health maintenance organization, bothersome stress urinary incontinence was reported in 15% of women and urgency incontinence/overactive bladder in 13% [***18:*** *Lawrence JM, et al. Prevalence and co-occurrence of pelvic floor disorders in community-dwelling women. Obstet Gynecol. 2008 Mar;111(3):678-85*]. The prevalence of urinary incontinence increases with age and is particularly high for individuals living in nursing homes, with rates ranging from 43-77% [***19:*** *Offermans MP, Du Moulin MF, Hamers JP, Dassen T, Halfens RJ. Prevalence of urinary incontinence and associated risk factors in nursing home residents: a systematic review. Neurourol Urodyn. 2009;28(4):288;* ***20:*** *Rortveit G, et al. Age- and type-dependent effects of parity on urinary incontinence: the Norwegian EPINCONT study. Obstet Gynecol. 2001;98(6):1004*]. Urinary incontinence is also common in persons with cognitive impairment/dementia, with the prevalence ranging from 10-38% [***21:*** *Drennan VM, et al. The prevalence of incontinence in people with cognitive impairment or dementia living at home: a systematic review. Neurourol Urodyn. 2013 Apr;32(4):314-24.*].

CLASSIFICATIONS AND ETIOLOGIES OF URINARY INCONTINENCE

The main types of urinary incontinence (UI) are stress, urgency and overflow incontinence. Many women have features of more than one type, therefore identification of UI classification helps guide the most appropriate therapy.

- **Stress urinary incontinence** (SUI) is the involuntary leakage of urine that occurs with increases in intra-abdominal pressure, such as with exertion/exercise, sneezing, coughing, laughing, in the absence of a bladder contraction. Stress incontinence is the most common type of UI in younger women, with the highest incidence in women ages 45 to 49 years old. Mechanisms of stress incontinence include urethral hypermobility and intrinsic sphincteric deficiency (ISD or type III SUI).

- **Urethral hypermobility** is thought to stem from inadequate support of the pelvic floor muscles and vaginal connective tissue to the urethra and bladder neck [***22:*** *Willsiam Gynecology, 2nd, Hoffman BL, Schorge JO, Schaffer JI, et al, Rahn DD, Wai CY. Urinary incontinence. (Eds), McGraw Hill Medical, New York 2012. p.609*]. This causes the urethra and bladder neck to lose the ability to close completely against the anterior vaginal wall. Thus, with an increase in intra-abdominal pressure, the muscular tube of the urethra fails to close adequately, leading to incontinence.

Risk factors that lead to insufficient urethral support from chronic pressure include high-impact activity, chronic cough, obesity, or trauma due to childbirth, especially operative vaginal deliveries (i.e., with the use of a vacuum or forceps). Childbirth can cause trauma directly to the pelvic muscles and may also damage nerves leading to pelvic muscle dysfunction. Treatments for hypermobility stress incontinence are aimed at providing a backboard of support for the urethra.

- **Intrinsic sphincteric deficiency (ISD)** is another form of stress urinary incontinence that results from a loss of urethral tone that normally keeps the urethra closed (versus in hypermobility, that results from a loss or reduction in strength of the supportive tissues). ISD, however, can occur in the presence or absence of urethral hypermobility, and typically results in severe urinary leakage even with very small amounts of increases in abdominal pressure. In general, ISD often results from neuromuscular damage and can be seen in women who have had multiple pelvic or incontinence surgeries. Therefore, it is challenging to treat women with ISD, and they usually have worse surgical outcomes [***23:*** *Lim YN, Dwyer PL Curr. Effectiveness of midurethral slings in intrinsic sphincteric-related stress urinary incontinence. Opin Obstet Gynecol. 2009;21(5):428;* ***24:****Schierlitz L, et al. Effectiveness of tension-free vaginal tape compared with transobturator tape in women with stress urinary incontinence and intrinsic sphincter deficiency: a randomized controlled trial. Obstet Gynecol. 2008;112(6):1253*].

- **Urgency urinary incontinence (UUI)** is the urge to void, immediately preceding or accompanied by involuntary leakage of urine. The amount of leakage ranges from a few drops to completely soaked undergarments. "Overactive bladder" or detrusor overactivity, is a term that describes the constellation of symptoms of urinary urgency with or without incontinence, which is often accompanied by nocturia (frequent nighttime urination) and urinary frequency [***25:*** *(Nygaard I. Clinical practice. Idiopathic urgency urinary incontinence. N Engl J Med. 2010;363(12):1156;* ***26:*** *Abrams P, et al. Members of Committees, Fourth International Consultation on Incontinence. Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. Neurourol Urodyn. 2010;29(1):213*].

Urgency incontinence is more common in older women and may be associated with co-morbid conditions that occur with age. It is believed to result from detrusor (bladder) muscle overactivity, leading to involuntary detrusor contractions during bladder

filling. This may be secondary to neurologic disorders (e.g., spinal cord injury), bladder abnormalities or may be idiopathic (unknown cause). The prevalence of detrusor overactivity, has been found in 21% of healthy, continent, community-dwelling elderly [***27:*** *Resnick, NM, Elbadawi, A, Yalla, SV. Age and the lower urinary tract: What is normal. Neurourol Urodynam. 1995; 14:577*].

- **Mixed urinary incontinence (MUI)** occurs when women exhibit symptoms of both stress and urgency urinary incontinence.

- **Overflow incontinence (OUI)** is UI demonstrated by continuous urinary leakage or dribbling in the setting of incomplete bladder emptying. Associated symptoms can include weak or intermittent urinary stream, hesitancy, frequency, and nocturia. When the bladder is very full, stress leakage can occur or mild bladder contractions can be triggered, leading to symptoms similar to SUI or UUI.

The two causes of OUI are detrusor underactivity or bladder outlet obstruction.

- **Detrusor underactivity** can be caused by either impaired contractility of the detrusor muscle or impaired urothelial sensory function. Studies have shown that detrusor contractility and efficiency decrease with age; approximately 5 to 10 percent of older adults have severe detrusor underactivity. There are several causes of detrusor underactivity such as smooth muscle damage, fibrosis, hypoestrogenism, peripheral neuropathy (as a result of diabetes mellitus, vitamin B12 deficiency, alcoholism) and damage to the spinal detrusor nerves (from spinal cord diseases, such as multiple sclerosis, spinal stenosis) [***28:*** *Smith PP; Neurourol Urodyn. Aging and the underactive detrusor: a failure of activity or activation? 2010;29(3):408;* ***29:*** *Taylor JA 3rd, Kuchel GA. Detrusor underactivity: Clinical features and pathogenesis of an underdiagnosed geriatric condition. J Am Geriatr Soc. 2006;54(12):1920;* ***30****: Panicker JN, et al. The possible role of opiates in women with chronic urinary retention: observations from a prospective clinical study. J Urol. 2012 Aug;188(2):480-4;* ***31:*** *Swinn MJ, Fowler CJ. Isolated urinary retention in young women, or Fowler's syndrome. Clin Auton Res. 2001 Oct;11(5):309-11*]. A small set of women with OUI can have detrusor hyperactivity with impaired contractility (DHIC), where the bladder does not effectively contract to empty while having low amplitude hyperactivity, resulting in urgency as well as overflow incontinence.

- **Bladder outlet obstruction** is generally caused by external compression of the urethra. The most common causes include fibroids, moderate to severe pelvic organ prolapse or overcorrection of the urethra from prior pelvic floor surgery. Less common causes include external masses at the level of the bladder outlet.

- **Other urologic/gynecologic disorders** include vaginal atrophy, urogenital fistulas, urethral diverticulae, and ectopic ureters; as well as neurologic disorders, such as

stroke, Parkinson's disease and normal pressure hydrocephalus, bladder cancer, or invasive cervical cancer.

Potentially reversible causes of UI

Reversible contributors to urinary incontinence include medications, alcohol and caffeine intake, constipation/stool impaction, and urinary tract infection (UTI). UTI may cause or worsen urinary incontinence. UTI should be treated before initiating further investigation or therapeutic intervention for UI [***32**: ACOG-AUGS committee opinion: Evaluation of uncomplicated stress urinary incontinence in women before surgical treatment; June 2014: CO 603*].

EVALUATION and CLINICAL TESTS

Only a few clinical tests are necessary for the initial evaluation of a woman with urinary incontinence, as conservative treatment can be initiated based on symptoms alone. It is not necessary to obtain radiographic imaging for the initial evaluation in patients without complex neurologic conditions or abnormal findings on physical examination.

- **Bladder stress test** is performed with the patient in the standing position with a comfortably full bladder. While the examiner visualizes the urethra by separating the labia, the patient is asked to Valsalva and/or cough vigorously. This can also be done while the patient is positioned lying down (lithotomy) during the exam. However, if not demonstrated in the lithotomy position, then she can stand.

- **Post-void residual (PVR)** is obtained via sterile catheterization or by bladder scan. Results of PVR testing are neither standardized nor well-evaluated. In general, a PVR of less than one-third of total voided volume is considered adequate emptying. Additional suggested parameters include a PVR of less than 50 mL as normal and a PVR greater than 200 mL as abnormal.

- **Urodynamic studies (UDS)** are somewhat invasive and are not necessary to initiate therapy. A 2013 systematic review of 99 studies including over 80,000 women found insufficient evidence to support the ability of UDS to predict the outcomes of nonsurgical treatment for stress incontinence [***33:** Huang AJ. Nonsurgical treatments for urinary incontinence in women: summary of primary findings and conclusions. JAMA Intern Med. 2013;173(15):1463*]. However, in women with suspected overflow incontinence (such as, underlying neurologic conditions, history of diabetes or by symptom history), urodynamic testing may be indicated for further evaluation.

- **Urethral mobility evaluation** is done at the time of the pelvic exam, where the urethral mobility is visually observed during a Valsalva maneuver. Generally, urethral

hypermobility is evident when there is a 30 degree or greater movement of the urethra from the horizontal axis.

ANALYSIS AND OPINIONS ON UI IMPACT ON HEALTH, EPIDEMIOLOGY, CLASSIFICATIONS, SURGICAL CANDIDATES

 Urinary incontinence is common in women. Risk factors for urinary incontinence include obesity, number of pregnancies, mode of delivery, older age and family history.

- The major clinical types of urinary incontinence are stress incontinence (leakage with maneuvers that increase intra-abdominal pressure), urgency incontinence (sudden urgency followed by leakage), mixed incontinence (symptoms of both stress and urgency) and overflow incontinence. "Overactive bladder" is a term that describes a syndrome of urinary urgency, with or without incontinence, nocturia and/or frequency.

- Other etiologies for urinary incontinence in women include other less common urologic or gynecologic disorders (e.g., urogenital fistulas, cancer), neurologic diseases (e.g., multiple sclerosis), and potentially reversible causes (caffeine, constipation).

- The initial evaluation includes a thorough history, physical examination, and urinalysis. The history should classify the type of incontinence, elicit possible underlying conditions, and identify potentially reversible causes of incontinence. The history should also prioritize the patient's urinary symptoms, as well as identify other symptoms that indicate the need to evaluate further for underlying causes of incontinence.

    - Women presenting with urinary incontinence should have a pelvic examination.
    - If a urinalysis shows suspicion of a urinary tract infection, then a urine culture should be obtained.
    - A bladder stress test is used to diagnose stress urinary incontinence. Post-void residual volume is also important in the evaluation. UDS are not routinely performed, but may aid in adequately evaluating a complex or unclear case.

CANDIDATES FOR SURGICAL TREATMENT

Women who are planning primary surgical treatment of SUI should undergo preoperative evaluation to reasonably exclude other etiologies of urinary incontinence and assess surgical risk.

Women who have persistent symptoms or women who decline conservative therapy.

In general, a trial of conservative therapy is advisable prior to surgical treatment because of its low risk profile. Conservative therapy for SUI includes pelvic muscle exercises (PME) with or without biofeedback or incontinence pessaries, medications, such as anti-muscarinics can be tried, but as a general rule, these will not help symptoms of SUI. However, some women ultimately need surgical intervention despite such conservative measures. In one study of 198 women treated with PME for SUI, women with severe stress incontinence, age <55 years, and higher educational level were more likely to go on to surgical treatment within 12 months of PME [***34:*** *Yip SK, Cardozo L. Psychological morbidity and female urinary incontinence. Best Pract Res Clin Obstet Gynaecol. 2007 Apr; 21(2):321-9. Epub 2007 Jan 3*].

For SUI, surgical treatments have consistently been shown to have a higher efficacy rate than conservative therapy (approximately 40% for PME, versus 70-80% for surgery). As an example, in the only randomized trial to compare surgical and conservative therapy for SUI, midurethral sling surgery compared with physiotherapy had a significantly higher subjective improvement rate (90.8 versus 64.4 percent) and objective cure rate (76.5 versus 58.8 percent) at 12-month follow-up [***35:*** *Ratner et al. Sexual satisfaction in the elderly female population: A special focus on women with gynecologic pathology. Maturitas. 2011 Nov;70(3):210-5. Epub 2011 Sep 22;* ***36:*** *Coyne KS, et el. The burden of lower urinary tract symptoms: evaluating the effect of LUTS on health-related quality of life, anxiety and depression: EpiLUTS. BJU Int. 2009 Apr;103 Suppl 3:4-11;* ***37:*** *Barber MD et al. Sexual function in women with urinary incontinence and pelvic organ prolapse. Continence Program for Women Research Group; Obstet Gynecol. 2002;99(2):281;* ***38:*** *Dubeau CE, Simon SE, Morris JN. The effect of urinary incontinence on quality of life in older nursing home residents. J Am Geriatr Soc. 2006;54(9):1325*]. However, SUI surgery is associated with increased morbidity, postoperative voiding difficulty, and development or worsening of urgency incontinence. Thus, surgical intervention is often reserved for those with persistent symptoms despite conservative therapy or for those that decline those therapies.

The following evaluation can be done before incontinence surgery in women with SUI:

- History
- urinalysis, as sometimes UTI can cause some UI
- physical examination
- demonstration of stress urinary incontinence
- assessment of urethral mobility, and
- measurement of post-void residual urine volume [***9***].

Women with mixed urinary incontinence (components of both stress and urgency incontinence) may benefit from a trial of anticholinergic medication if urgency symptoms are the more bothersome component. Reduction of urgency symptoms may help the patient sufficiently to avoid surgery for the concomitant stress incontinence symptoms.

However, in these women with MUI, a UDS will probably be an important diagnostic test that should be done prior to surgery.

Women with occult SUI.

Advanced pelvic organ prolapse (POP) and SUI commonly co-exist; however, in many women, the SUI may become apparent only when the prolapse has been corrected. This phenomenon is known as occult SUI and is not always reliably predicted by pre-operative UDS with prolapse reduction. However, a pre-op UDS with prolapse reduction should still be implemented in order to give the patient some data that she may want to consider when determining if she would like a "prophylactic" anti-incontinence procedure. The Cleveland Clinic has developed a risk calculator that will provide data regarding the predictive percentage for the development of "de novo" (new onset) UI, after POP surgery, with and without a concomitant anti-incontinence surgical procedure. The information needed to determine these percentages includes: age, BMI, number of vaginal births, presence or absence of diabetes, UUI and stress test results [***39:*** *Jelovsek JE, et al. Pelvic Floor Disorders Network. A model for predicting the risk of de novo stress urinary incontinence in women undergoing pelvic organ prolapse surgery. Obstet Gynecol. 2014 Feb;123(2 Pt 1):279-87. Web address: http://www.r-calc.com/administratorcalculatorGridPreview.aspxisGrid=1&mobile=0&isTemp=0&calculator_grid_id=b8aa31f8-6023-493f-87bd-7d5c6553af91*].

Women finished with childbearing.

Since pelvic support may be disrupted during pregnancy, and particularly following a vaginal birth, most physicians recommend delaying surgical management of SUI until childbearing has been completed. The best choice for mode of delivery is uncertain in women who have undergone prior anti-incontinence surgery. A review of case reports suggested that vaginal delivery was associated with a higher risk of recurrent incontinence than cesarean delivery, but no significant difference was found in a survey of physicians who had performed 3400 retropubic or transobturator midurethral sling procedures (vaginal delivery: 20%; cesarean: 13%). Women of childbearing age who elect surgical treatment should be counseled on the lack of data regarding the preferred mode of delivery and the risk of recurrent incontinence following delivery [***40:*** *Serati M, et al. Female urinary incontinence during intercourse: a review on an understudied problem for women's sexuality. J Sex Med. 2009;6(1):40;* ***41:*** *Panel L, et al. Int Urogynecol J Pelvic Floor Dysfunct. How to advise a woman who wants to get pregnant after a sub-urethral tape placement? 2008;19(3):347;* ***42:*** *Dainer M, Hall CD, Choe J, Bhatia N. Pregnancy following incontinence surgery. Int Urogynecol J Pelvic Floor Dysfunct. 1998;9(6):385;* ***43:*** *Brown JS, et al. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc. 2000;48(7):721*].

TREATMENT OF STRESS URINARY INCONTINENCE

Initial Treatment

This typically includes lifestyle modifications and pelvic floor muscle exercise, that can be implemented in all patients with all types of urinary incontinence, whether it be stress, urgency, or a combination of the two. In addition, bladder training can be implemented in those with urgency incontinence, and in some women with stress incontinence [***26:*** *Abrams P* ***2010; 44:*** *Harris et al. Care seeking and treatment for urinary incontinence in a diverse population. J Urol 2007;177(2):680;* ***45:*** *The Norwegian EPINCONT Study, Hannestad et al. Help-seeking and associated factors in female urinary incontinence. Scand J Prim Health Care. 2002 Jun;20(2):102-7.;* ***46:*** *Morrill et al. Seeking healthcare for pelvic floor disorders: a population-based study. Am J Obstet Gynecol. 2007 Jul;197(1):86.e1-6*]. An ideal trial period for conservative therapies is approximately six weeks. It is certainly reasonable to treat with conservative therapies for up to 12 weeks, especially in those patients who need to and are willing to lose weight.

Adjusting etiologic/aggravating factors

Causative or exacerbating factors of urinary incontinence, such as medical conditions (neurologic disorders and cancer for example), as well as medications (such as diuretics) should be corrected or modified; if possible, as part of the initial management of urinary incontinence [***48:*** *Coyne et al. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study; BJU Int. 2008;101(11):1388*].

Lifestyle modification

- Weight loss, if applicable, can make a significant change/ improvement in urinary incontinence. For example, one randomized trial of 338 overweight and obese women (mean body mass index 36 kg/m2) found that weekly incontinence episodes decreased in patients assigned to an intensive six-month weight loss program compared with a control group (47 versus 28 percent) [***49:*** *Subak LL, et al. Weight loss to treat urinary incontinence in overweight and obese women. PRIDE Investigators N Engl J Med. 2009;360(5):481;* ***50:*** *Brown JS, et al. Lifestyle intervention is associated with lower prevalence of urinary incontinence: the Diabetes Prevention Program. Diabetes Prevention Program Research Group Diabetes Care. 2006;29(2):385;* ***51:*** *Wing RR, et al. Effect of weight loss on urinary incontinence in overweight and obese women: results at 12 and 18 months. Program to Reduce Incontinence by Diet and Exercise Group J Urol. 2010;184(3):1005.);* ***52:*** *Phelan S, et al. Weight loss prevents urinary incontinence in women with type 2 diabetes: results from the Look AHEAD trial. Look AHEAD Research Group J Urol. 2012;187(3):939*].

- Reducing or eliminating bladder irritants, such as citrus foods, spicy foods, caffeinated products, carbonated beverages, and alcohol (to name a few) [***53:*** *Gleason JL, et al. Caffeine and urinary incontinence in US women. Markland AD Int Urogynecol J. 2013*

Feb;24(2):295-302; ***54:*** *Dallosso HM, et al. The association of diet and other lifestyle factors with overactive bladder and stress incontinence: a longitudinal study in women. Leicestershire MRC Incontinence Study Group. BJU Int. 2003 Jul;92(1):69-77*].

- Establishing a daily bowel regimen to reduce constipation, as it can exacerbate urinary incontinence [***55:*** *Wood LN, Anger JJ. Urinary incontinence in women. BMJ. 2014;349:g4531*].

- Discontinuance of smoking, as smoking has been associated with an increased risk for urinary incontinence [***54:*** *Dallosso 2003****; 56:*** *Tähtinen RM, et al. Smoking and bladder symptoms in women. Obstet Gynecol. 2011 Sep;118(3):643-8.*].

Pelvic floor muscle exercises (Kegel exercises)

Pelvic floor muscle (Kegel) exercises or pelvic floor muscle therapy (PFMT), function to strengthen the pelvic floor musculature to provide a backboard for the urethra to compress on and to reflexively inhibit detrusor contractions and thus, urine flow. If women are able to perform Kegel exercises appropriately, then verbal instruction on timing and frequency of exercise is usually adequate. However, many women have difficulty identifying the proper muscles, therefore referral to an occupational or physical therapist that is specialized in pelvic floor dysfunction can be implemented. The therapist can assist in pelvic floor dysfunction with the modalities of supervised physical therapy, vaginal weighted cones and/ or biofeedback. Systematic reviews of randomized trials have found that compared with no treatment, women treated with pelvic muscle exercises were more likely to report improvement [***57:*** *Dumoulin C, Hay-Smith EJ, Mac Habée-Séguin G. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev 2014;* ***58****: Shamliyan TA, et al. Systematic review: randomized, controlled trials of nonsurgical treatments for urinary incontinence in women. Ann Intern Med. 2008;148(6):459; 19*].

- With supervised pelvic floor physical therapy, specific instruction by health professionals, along with patient regular performance works best.

- However, time and/or the cost of pelvic floor physical therapy may be prohibitive. Therefore, weighted vaginal cones can be used. The woman inserts the cone in her vagina and uses pelvic muscle contractions to hold it in place during activity. In a 2013 systematic review and meta-analysis of over 20 small randomized trials, researchers found some evidence that cones have increased efficacy over no active treatment, but there was not conclusive evidence that they provide increased efficacy over standard pelvic floor muscle exercises [***59:*** *Herbison GP, Dean N. Weighted vaginal cones for urinary incontinence. Cochrane Database Syst Rev. 2013;7*].

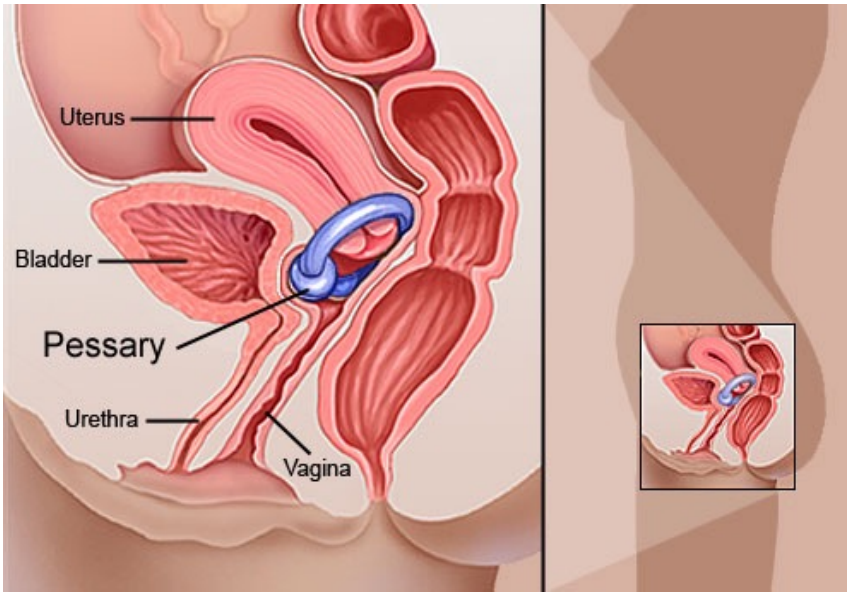
- Biofeedback involves placement of a vaginal pressure sensor within the vagina, which measures pressure and provides an audible or visual feedback of the strength of the pelvic floor contraction. Biofeedback can also be done using electrical stimulation, via a plated probe that is placed in the vagina or anal canal and provides a small electrical current to stimulate the pelvic floor muscles to contract. In a 2012 review of 9 studies, it was found that compared with sham stimulation, this type of biofeedback improved continence rates for women with urgency, stress, or mixed incontinence [***60:*** *Effective Health Care Program. Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness. Agency for Healthcare Research Quality 2012*].

Bladder training is most effective for women with urgency incontinence [***60*** *Effective Health Care Program 2012*], but some women with stress incontinence (at higher bladder volumes) might also benefit from the timed voiding component. Bladder training starts with timed voiding, where a patient is instructed to void by the clock at regular intervals, using the shortest interval that she can tolerate without a leak. Once she can go 2 days without leakage, the time between scheduled voids is increased.

Vaginal estrogen therapy for peri- or postmenopausal women with either stress or urgency incontinence and vaginal atrophy is another available treatment option. Vaginal atrophy can lead to symptoms of urinary frequency and dysuria, and can contribute to incontinence [***61:*** *Emily S Lukacz, MD, MAS. Initial treatment of SUI, other modalities; uptodate.com: Literature review current through: Jul 2015*]. The patient must be counseled that it can take up to three months for patients to notice benefits from treatment.

Pessary Use

A pessary is a rubber or silicone device that is fitted for the patient's anatomy, typically in those patients with pelvic organ prolapse. Continence pessaries may be used for women with stress incontinence as an adjunct or substitute for pelvic muscle exercises. However, the overall success rate is only about 50% [***62:*** *Richter HE, et al. Pelvic Floor Disorders Network. Continence pessary compared with behavioral therapy or combined therapy for stress incontinence: a randomized controlled trial. Obstet Gynecol. 2010;115(3):609*] (see pictorials below).



Pharmacologic Therapy

Multiple medications have been evaluated for stress incontinence in women [***63:*** *Malallah MA, Al-Shaiji TF. Pharmacological treatment of pure stress urinary incontinence: a narrative review. Int Urogynecol J. 2015 Apr;26(4):477-85. Epub 2015 Jan 29*]. However, in the United States, no pharmacologic therapies have been approved by the US Food and Drug Administration (FDA) for treatment of stress incontinence.

Duloxetine (brand name, Cymbalta) is a serotonin and norepinephrine reuptake inhibitor which has been used as treatment for stress incontinence. If patients are already being treated for depression, it might be the medication used primarily to treat her depression, with a side benefit of improving her stress urinary incontinence. However, a 2012 systematic review of 24 studies (including six randomized trials) found that duloxetine was not more effective than placebo for stress incontinence [***59***].

Alpha-adrenergic agonists (e.g., phenylpropanolamine), which theoretically should help in UI, as they stimulate urethral smooth muscle contraction, but they are not recommended because they have shown minimal efficacy compared with placebo and have a high rate of adverse effects [***63:*** *Mallah 2015****; 64:*** *Zinner NR, Koke SC, Viktrup L. Pharmacotherapy for stress urinary incontinence : present and future options. Drugs. 2004;64(14):1503-16*].

Mechanical Devices

Various types of mechanical devices that are placed within the vagina or urethra to prevent urinary leakage have been studied over the years, but their success has been low with the high rates of urinary tract infections and lack of evidence regarding long-term safety and efficacy. Examples of these intravaginal devices include: intravaginal sponge,

vaginal loop (with thread for removal), vaginal continence dish/ ring, Hodge pessary, continence tampon and continence guard. Intrauretral devices include: urethral plug, Reliance urinary control device, FemAssist and New Expandable assist Tip (NEAT) device. A total of eight trials involving 787 women were reviewed. Three trials compared a mechanical device with no treatment and although suggesting that use of a mechanical device might be better than no treatment, the evidence was inconclusive. Four trials compared one mechanical device with another. Data from the individual trials showed no clear difference between devices. Although there were several types of mechanical devices used in these studies, including different versions of each device, few are commercially available. Many devices seem to have been developed but never withstood the test of time, the authors speculated that the lack of good quality supportive clinical trial data was a contributory factor, as well as the fact that women do not like using a mechanical device and would prefer to use the other available options such as PFMT or surgery [***65:*** *Lipp A, Shaw C, Glavind K. Cochrane. Mechanical devices for urinary incontinence in women. Database Syst Rev. 2014;12:CD001756*].

Surgical Options

Women without sufficient improvement with the initial treatments delineated above, or who choose not to proceed with conservative measures, should be evaluated for surgical therapy. Surgery offers high cure rates for stress urinary incontinence (SUI), even in older women. A randomized trial comparing pelvic floor muscle training with surgery found improved overall outcomes with surgery, with nearly 50 percent of women assigned to conservative therapy crossing over to surgery [***66:****Labrie J, et al. Surgery versus physiotherapy for stress urinary incontinence. N Engl J Med. 2013 Sep;369(12):1124-33*].

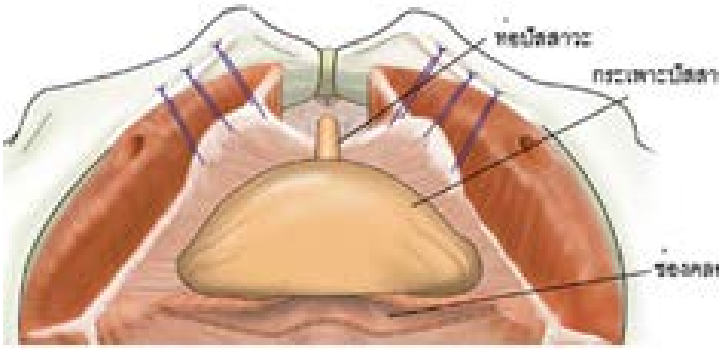
Prior Gold Standard Surgical Treatments

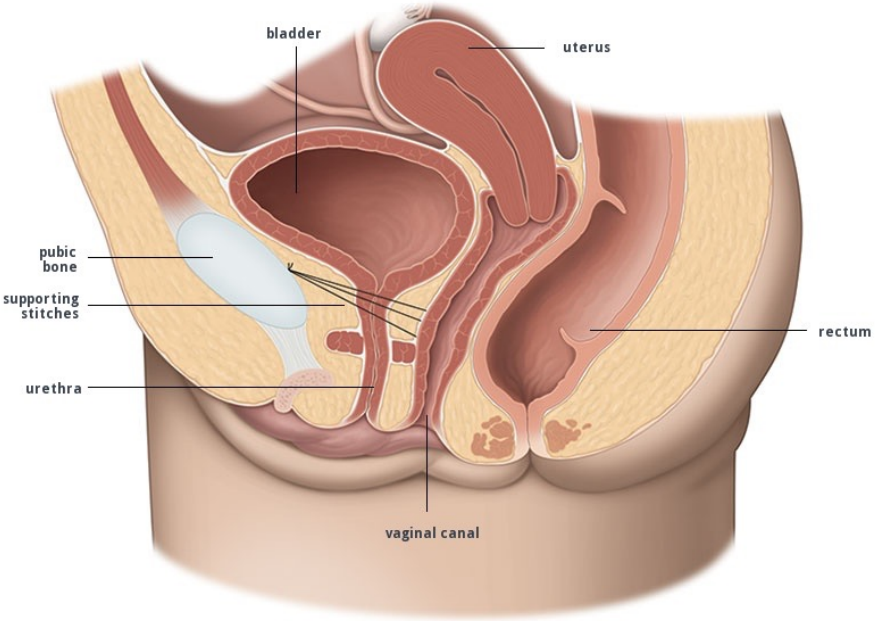
Many surgical options exist for women with SUI. Traditionally, the gold standard has been the Burch Retropubic Urethropexy and Autologous Pubovaginal Slings. However, over the last 10 years procedures to treat SUI have greatly evolved. These prior procedures do still remain appropriate treatment options for some patients, but are no longer the gold first-line standard for surgical management of SUI [***10:*** *Cox 2013***]**.

Burch Retropubic Urethropexy (BRU)

In the classic Burch retropubic urethropexy, there is trans-abdominal incision of approximately 12-14 cm or approximately 5 inches, that typically requires a 6 week period of healing. The procedure involves placement of 2 bilateral non-absorbable (permanent) sutures through the pubocervical fascia at the level of the midurethra and urethrovesical junction (UVJ), which are then fixed to Cooper's ligament (see pictorials below). Burch retropubic urethropexy might be considered for women undergoing a simul-

taneous open (not laparoscopic or robotic) surgery, such as pelvic organ prolapse surgery or hysterectomy.

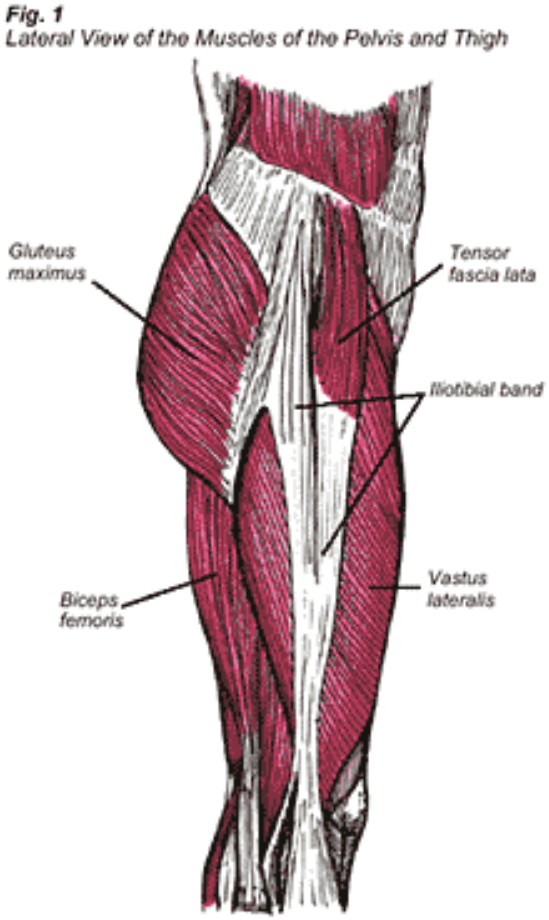


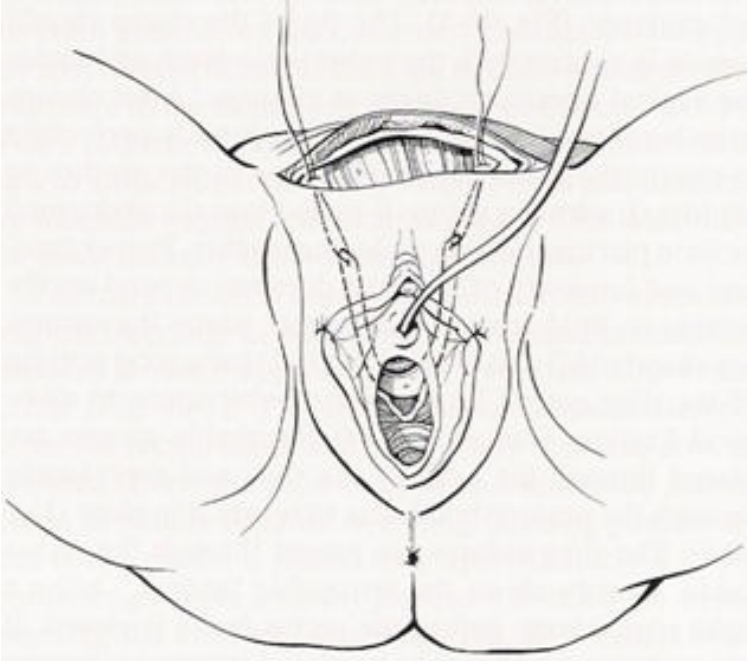


Pubovaginal Fascial Sling (PFS)

A pubovaginal fascial sling is a surgical procedure that places a band of sling material (traditionally has been autologous fascia) is placed directly under the bladder neck

(i.e., proximal urethra) or mid-urethra, anchored with permanent suture. The sling can be harvested from the rectus abdominus fascia, which involves a 10-12 cm abdominal incision; or the tensor fascia lata, from the lateral thigh, which involves a 5-6 cm transverse incision of the distal thigh (see pictorial below). This again typically requires a 6 week period of healing.





In assessing efficacy and complications of the prior gold standard surgical treatments for SUI, the following is a summary.

Efficacy

In a long-term observational study, comparing BRU and PFS, continence rates at 5 years were 24.1% vs 30.8%, respectively [***67:*** *Brubaker L, et al. Urinary Incontinence Treatment Network. Complications in women undergoing Burch colposuspension versus autologous rectus fascial sling for stress urinary incontinence. J Urol. 2009 May;181(5):2192-7*].

Complications

- De novo enterocele rates as high as 14% following Burch colposuspension have been observed [***68:*** *Chalila C, Stanton SL. Complications of surgery for genuine stress incontinence. British Journal of Obstetrics and Gynecology. Dec 1999 (106): 1238-1245*]; ***69:*** *Jirschele K, Seitz M, Zhou Y, Rosenblatt P, Culligan P. A multicenter, prospective trial to evaluate mesh-augmented sacrospinous hysteropexy for uterovaginal prolapse. Int Urogynecol J. 2015 May;26(5):743-8*]. This is thought to occur as a result of the more anterior angulation of the vagina as a result of the procedure, allowing the posterior compartment to become more subject to the pressure transmission of intra-abdominal pressure.

- In patients who underwent BRU, rates of worsening of apical prolapse increased from 21% preoperatively to 63% at 24 months; 18% of the women with prolapse were symptomatic.

- Postoperatively, there was a 37.3% midline or apical prolapse rate, a 2.7% rate of dyspareunia and a 6.8% rate of groin or suprapubic pain in the BRU patients [***70:***

Demirci F, et al. Long-term results of Burch colposuspension. Gynecol Obstet Invest. 2001 51: 243-7].

 Urinary retention – One trial of 655 women randomized to bladder neck sling or Burch procedure reported greater urinary retention rates for the bladder neck sling patients than the Burch patients (66% versus 42%) [***71:*** *Albo ME, et al. Urinary Incontinence Treatment Network. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med. 2007;356(21):2143*].

 Postoperative urinary urge incontinence ranges from 18 to 40% [***72****: Ulmsten U and Petros P (1995) Intravaginal slingplasty (IVS): an ambulatory surgical procedure for treatment of female urinary incontinence. Scand J Urol Nephrol 29: 75-82;* **73***: Athanasopoulos A, Gyftopoulos K, McGuire EJ. Efficacy and preoperative prognostic factors of autologous fascia rectus sling for treatment of female stress urinary incontinence. Urology. 2011 Nov;78(5):1034-83.****75****: Rapp, K, et al. Risk factors associated with urge incontinence after continence surgery. J Urol. 2009;182(6):2805*]. In one study, women who had a bladder neck sling compared with women who had Burch procedure were almost twice as likely to receive treatment for postoperative urge urinary incontinence six weeks after surgery [***75****: Rapp 2009*].

 Voiding dysfunction – Voiding dysfunction after bladder neck sling ranges from 10 to 14% in the first six to eight weeks after surgery [***71:*** *Albo 2007****; 73:*** *Athanasopoulos 2011;* ***76:*** *Chai TC, et al, Urinary Incontinence Treatment Network. Complications in women undergoing Burch colposuspension versus autologous rectus fascial sling for stress urinary incontinence. J Urol. 2009 May;181(5):2192-7*].

 Urinary function complications included: prolonged voiding dysfunction (2%) and new onset urgency incontinence (3%) [***67*** *Brubaker 2012*].

 The AUA Guidelines showed Burch patients had a median 8% rate of de novo urge incontinence 12-23 months post-op, and a median 17% rate of persistent UUI. [***77****: Appell RA, et al. Guideline for the Surgical Management of Female SUI: 2009 Update, Revised 2012 AUA Education & Research Inc 1-14*].

 In the 2014 SGS Systematic Review, higher rates of hematoma formation were seen with Burch than retropubic MUS, as well as a higher wound infection rate [***78****: Schimpf MO, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Society of Gynecologic Surgeons Systematic Review Group Am J Obstet Gynecol. 2014 Jul;211(1):71.e1-71.e27*].

 Incidental cystotomy (3%) in BRU. For PFS, at the time of rectus fascial sling ranges from 1 to 3% [***71:*** *Albo 2007;* ***79****: Broussard AP, Reddy TG, Frilot CF 2nd, Kubricht WS 3rd, Gomelsky Long-term follow-up of porcine dermis pubovaginal slings. A Int Urogynecol J. 2013;24(4):583.*]. Bladder perforation is lower with rectus fascial sling compared with retropubic midurethral sling [***80:*** *Richter HE, et al. Continence pessary compared with behavioral therapy or combined therapy for stress incontinence: a randomized controlled trial. Obstet Gy-*

necol. 2010;115(3):609].This is possibly because of the more extensive dissection with suburethral rectus fascial sling.

- Other complications of BRU: surgical wound complications requiring surgery (2.4%), recurrent cystitis leading to diagnostic cystoscopy (1.5%), bleeding (1%), ureteral injury (1%), incidental vaginotomy (0.5%), ureteral vaginal fistula (0.5 percent), erosion of suture into the bladder (0.5%) due to permanent suture used, and pyelonephritis (0.5%) [***67:*** *Brubaker 2012;* ***76:****Chai 2009*].

- Minor complications or adverse events after autologous fascia bladder neck sling can range from 29 to 6%, while serious adverse events in one randomized trial occurred in 13% [***71:*** *Albo 2007;* ***73:*** *Athanasopoulos 2011 Nov;78(5):1034-83*].

The New Gold Standard Surgical Treatment

Midurethral Sling (MUS)

The mid-urethral sling (MUS) is now considered the new gold standard for surgical treatment of SUI. From a physiologic perspective, if the SUI is of the hypermobility type, then the treatments should be aimed at correcting it by providing a backboard of support for the urethra, which is what the MUS does.

The MUS involves the passage of a small strip of tape at the level of the mid-urethra, that serves as a "backboard" to compress this weakened urethral area during a Valsalva (or pressure inducing maneuver, such as coughing, lifting and/or exercise, etc.), in order to prevent leakage.

Keys points regarding the MUS briefly mentioned, include (which will be further discussed in detail later):

- Ulmsten and Petros [***72:****Ulmsten 1995*] first described outcomes of 50 patients after transvaginal tape (TVT)/sling placement performed via a minimally invasive technique in 1995 [***81****: Petros PE and Ulmsten UI (1997) An integral theory of female urinary incontinence: experimental and clinical considerations. Acta Obstet Gynecol Scand 166 (Suppl): 3-8*].

- The concept of this surgical procedure was based upon the integral theory, which proposes that a physiologic 'backboard' is created through fixation of the middle region of the urethra to the pubic bone, via the pubourethral ligaments; which is a factor critical for the mechanism of continence [***72*** *Ulsten 1995*].

- Advantages over prior SUI surgical procedures include: good rationale based upon many years of serious scientific research; minimally invasive, could be performed un-

der local anesthesia, short duration procedure, relatively easy to perform; and at the time, had very good short and long term efficacy .

- When comparing the MUS with the PFS, the MUS was shown to have higher rates of urinary continence (UC), patient satisfaction and less urethrolysis [***82*** *:Trabuco, et al Medium-term comparison of continence rates after rectus fascia or MUS placement. AJOG, Mar 2009: 300-02*].

- MUS is the most commonly performed surgery to treat SUI in women.

- They have a good safety profile *[**14:** Wagner 1998*].

- The evidence supporting use of MUS is of high quality [***78:*** *Schimpf 2014*].

- Mid-urethral slings are considered the "new gold standard first line surgical treatment for women with SUI [***10:*** *Cox 2013*].

These are surgical procedures that female urologists, gynecologists, and urogynecologists (or female pelvic medicine and reconstructive surgeons) are expected to be competent to perform per residency and fellowship curriculum, as well as Board Certifications. As noted in ACGME Program Requirements for Graduate Medical Education in Female Pelvic Medicine and Reconstructive Surgery, a fellow must demonstrate competence in assessing the effects of treatment, recognizing and managing the complications of therapy, diagnosing and managing patients with urinary incontinence, pelvic organ prolapse… In addition, a fellow must demonstrate competence in the behavioral, pharmacological, functional, non-surgical and surgical treatment of urinary incontinence, micturition disorders and pelvic organ prolapse [***83:*** *http://www.acgme.org/acgmeweb/Portals/0/PFAssets/ProgramRequirements/221-486_female_pelvic_med_07012014.pdf*].

KINDS OF SURGICAL RECONSTRUCTIVE MATERIALS

The four kinds of surgical reconstructive materials differ by source: synthetic mesh, autografts, allografts, and xenografts. The following is a comparison of reconstructive materials [***84****: Trabuco EC, Gebhart JB. Reconstructive materials used in surgery: Classification and host response. Literature review current through: Jul 2015*].

Synthetic

Types: available as both absorbable (such as, polyglactin 910 [Vicryl], polyglycolic acid [Dexon]) and nonabsorbable mesh (such as, polypropylene [Marlex, Prolene], and expanded polytetrafluoroethylene [ePTFE, Gore-Tex]).

It is accessible, easy to manufacture and obtain; materials are reproducible; ddurable; and cost-effective, as it is less expensive to produce than allo- and xenografts.

The macroporosity of the PP mesh allows for entry of fibroblasts, macrophages, blood vessels, and collagen fibers, in addition to tissue generation and subsequently, reduction in the risk of infection. These results are predictable and reproducible.

The infection rate is greater in microporous and multifilament grafts; there is a small risk of vaginal and/ or other organ mesh exposure and erosion (however, occurring less in the macroporous, monofilament graft types).

Autograft

Types: materials are harvested from the patient who is undergoing the procedure. Fascia lata and rectus fascia, the most commonly used autografts for slings. They have been used for decades and yield predictable results [***70:*** *Demirci 2001*]. It has been used because there is no risk of rejection; and no mesh exposure/ erosion, however, permanent sutures used to suture the mesh may erode. Since the graft is autologous, it is cost-effective, although additional operative time (which is costly) in harvesting the material increases.

There is limited tissue quantity and quality, and its use causes additional risks of pain, bleeding, infection, hernia formation, as the tissue needs to be harvested from the patient. In addition, the quality may not be as ideal as a non-autologous graft. The fascia is being derived from the very same patient, who has already demonstrated that her tissue is probably of poor strength factors, since her own tissue has failed to provide the supportive factors needed to maintain continence.

Allograft

Types: processed cadaveric fascia lata or acellular extracts of collagen, harvested from the dermis of human donors. Washing processes, are designed to remove cellular debris without permanently damaging the connective tissue scaffold. Human donors with risk factors or who test positive for HIV, syphilis, HTLV, or hepatitis B or C are excluded.

It is accessible, at least when compared to autografts (but is donor supply dependent). There are not additional host risks incurred from harvesting and the erosion risk is lower.

There is a potential for infection from transmission of host pathogens. There is also a possible risk of rejection. Strength inconsistencies of graft also occur and they are less durable as weakening of graft material occurs with processing. In addition, it can un-

dergo autolysis. Fitzgerald and associates found that upon re-operating on freeze-dried cadaveric fascial sling failures, the slings had undergone some form of degeneration or autolysis, and in some cases the sling could not be identified [***74*** *Fitzgerald MP, Mollenhauer J, BrubakerL. Failure of allograft suburethral slings. BJU Int 1999; 84: 785-88*].

Additionally, it is expensive and there is a limited donor pool.

Xenograft

Types: acellular extracts of collagen with or without additional extracellular matrix components that are harvested from non-human sources. Source species are bovine or porcine; site of harvest can be pericardium, dermis, or small intestine submucosa; and processing can be by the use or non-use of crosslinking [***85:****Trabuco EC, Klingele CJ, Gebhart JB. Xenograft use in reconstructive pelvic surgery: a review of the literature. Int Urogynecol J Pelvic Floor Dysfunct. 2007;18(5):555*].

It is more available, with larger quantities than autografts. There are no additional host risks incurred from harvesting and erosion risk is lower.

There is an additional infection risk from transmission of host pathogens and a possible risk of rejection. There are also strength inconsistencies of graft, with less durability given the weakening of graft material with processing. A small histopathologic study evaluated women who had undergone placement of a midurethral sling using a crosslinked porcine dermal collagen implant (Pelvicol) and who required sling revision due to recurrent stress urinary incontinence or urinary retention [***86:****Gandhi S, Kubba LM, Abramov Y, Botros SM, Goldberg RP, Victor TA, Sand PK. Histopathologic changes of porcine dermis xenografts for transvaginal suburethral slings. Am J Obstet Gynecol. 2005;192(5):1643*].Time from graft placement to biopsy ranged from 15 to 67 months. Although the graft remained encapsulated in the early biopsy specimens, there was a progressive increase in the immunologic response at the graft-host interface at 21 weeks. Histiocyte and multinucleated giant cell infiltration of the graft was detected by 42 weeks [***86***]. No residual graft was found in the 58- and 67-week samples, suggesting that the materials were resorbed in the interim [***86:*** *Gandhi 2005****, 85*** *Trabuco2007*]. In another study, women who had a Pelvicol reinforced posterior repair were evaluated upon reoperation one year postoperatively; no residual Pelvicol was found [***87****Altman D, et al. Functional and anatomic outcome after transvaginal rectocele repair using collagen mesh: a prospective study. Dis Colon Rectum. 2005;48(6):1233*].

Certain cultural or religious objections exist, especially in those who believe that all living creatures should not be harmed. Obtaining graft material from animals would be considered an act against very strong beliefs, thus would be an unacceptable option to that particular cultural or religious sector.

HOST RESPONSE

Histologic behavior to a class of material depends upon the physical and structural properties of the prosthesis. The type of histologic behavior to a class of material or the host response, is a key determinant of synthetic mesh related complications. For example, the risk of mesh exposure was 4.2 times greater for those who had polytetrafluoroethylene (PTFE) compared to those that used non-PTFE mesh, in patients undergoing a sacrocolpopexy [***88:*** *Cundiff GW, et al. Pelvic Floor Disorders Network. Risk factors for mesh/suture erosion following sacral colpopexy. Am J Obstet Gynecol. 2008;199(6):688.e1*].

Types of host responses.

Host response to reconstructive materials is described as the following:

- Incorporation is the neovascularization (new vessel formation) and collagen deposition throughout the graft material by host cells.

- Encapsulation is the collagen and connective tissue deposition at the periphery of the graft material by host cells.

- Mixed response is a combination of the two responses above; i.e., incorporation throughout the graft (specifically, the pores) and encapsulation at the periphery or remaining material.

- Resorption is the replacement of the graft material by host neo-connective tissue.

Theoretically, a mixed response may tend to have an increased risk of infection and erosion, from incorporation throughout the graft, as well as deposition at its edges. Clinically, however, prosthetic material related complications occur in three primary ways: exposure (tends to be mostly asymptomatic), infection (typically, an exposed, symptomatic prosthetic) and erosion (symptomatic material exposure). It is unusual for unexposed material to become infected. In my experience, I have not seen unexposed, or even exposed material become infected. Often times, in areas, such as the vagina, it may not be obvious as to whether it is true infection versus normal colonization. In addition, clinical manifestations may not be related to the graft material, but due to the quality of the host (for example, vaginal atrophy or poor connective tissue) or technique used (for example, mucosal only versus greater thickness [mucosal & submucosal] vaginal flaps) [***89:*** *Iglesia CB et al. The use of mesh in gynecologic surgery. Int Urogynecol J Pelvic Floor Dysfunct. 1997;8(2):105; 15: Mesh-related infections after pelvic organ prolapse repair surgery. Eur J Obstet Gynecol Reprod Biol. 2007;134(2):147*].

Critical host response factors.

In order to achieve the best host response to the reconstructive materials, the following factors need to be optimized. For synthetic mesh, pore size (space between fibrils); weave (mono vs. multifilament); weight (or the density); and absorption (absorbable vs non absorbable) are the critical factors of the graft material.

For xenografts, removal of host cellular components and chemically cross-linking are the critical factors. All of the above mentioned factors do not apply to autografts. It has not been effectively determined in allografts.

Pore size and weave

In synthetic material, pore size and weave influences cellular infiltration, risk of infection, mesh density and flexibility [***89:*** *Iglesia 2007*]. In animal studies, macropores (>75 microns; 1 mm = 1000 microns) allow for host cell colonization with collagen deposition and angiogenesis. In-vivo studies show that this allows **un**restricted immune cell access, therefore reducing the infection risk.

In animal studies, micropores (<10 microns) result in restriction of immune cell access because large immune cells (macrophages and natural killer cells, with a mean diameter of 9 to 20 microns) cannot infiltrate through the pores; while problematic bacteria (<1 micron) can [***90:*** *Cobb, et al. Textile analysis of heavy weight, mid-weight, and light weight polypropylene mesh in a porcine ventral hernia model. J Surg Res. 2006;136(1):1*].

Mesh weight, or density

When referring to mesh, the weight is a measure of how much material is needed to produce a given amount of the material.

Weight and elasticity are determined by pore size. Meshes with larger pores tend to be of a smaller weight and more elastic, versus the smaller-pored meshes which are of larger weight and less elastic. With larger pores, there is less material content and more flexibility rendered to the scar [***90:*** *Cobb 2006*]. This has led to the conclusion that lightweight materials have a lower rate of infection and/or erosion than heavier weighted graft materials. TRUE infection contributed by mesh is very, very low. One must keep in mind that the TVT width is only ONE centimeter, so very little material is implanted. There has been a movement toward lighter mesh in order to reduce the risk of infection, pain and erosion. However, this is primarily in the arena of prolapse and/or large hernia repairs, which require a larger amount of mesh material. This does not carry the same benefits directly for a small piece used for incontinence, which is treating a functional defect and NOT a large anatomical defect. Ethicon TVT weighs approximately 100 gm/m2 [***91***: *Moalli PA1. Tensile properties of five commonly used mid-urethral slings relative to the TVT. Int Uro-*

gynecol J Pelvic Floor Dysfunct. 2008 May;19(5):655-63], and has a pore size of 1379 microns (well above 75 microns, which is considered a macropore). There is a need for an optimal weight/density, such that if it is too light, then there is a loss in the efficacy of its intended function. Treating an anatomical problem versus a functional problem requires different specifications, as in the case of treating prolapse versus incontinence. An ultra- light-weight mesh may work well to improve the anatomic defect of prolapse, but would not accomplish improvement in the functional defect of incontinence. The latter is best accomplished by a lightweight mesh like the TVT mesh.

Mesh absorption

A "middle of the road approach," with partially absorbable materials (such as polypropylene with polyglactin [Vypro] or with poliglecaprone-25 [Ultrapro]), has been developed for use outside the context of SUI treatment, with the goal of reduced risk of mesh erosion and infection, but a greater durability than the completely absorbable products. There is little evidence regarding its efficacy clinically [***92:*** *Bellón JM, et al. Am J Surg. 2007;194(1):68;* ***93:*** *Achtari C, et al. Risk factors for mesh erosion after transvaginal surgery using polypropylene (Atrium) or composite polypropylene/polyglactin 910 (Vypro II) mesh. Int Urogynecol J Pelvic Floor Dysfunct. 2005;16(5):38;* ***93.1****: Barbolt TA. Biology of polypropylene/polyglactin 910 grafts. Int Urogynecol J Pelvic Floor Dysfunct. 2006;17 Suppl 1:S26*]. And in fact, high rates of erosion and problems of cicatrization were observed. Thus, the use of a half absorbable mesh does not seem to reduce the inflammation and could even accentuate it. On another note, in regards to the TVT, good efficacy results of the TVT procedure does not seem to be modified much by the additional procedure for prolapse [***94:*** *Denis S1 , et al. POP treatment by the vaginal route using a Vypro composite mesh; preliminary results. ICS IUGA abstract 620, 2004*]. When comparing 3 different types of synthetics (Vypro {semi-absorbable multifilament; non-absorbable polypropylene plus absorbable polyglactin}vs. Ultrapro mesh {semi-absorbable monofilament; non-absorbable polypropylene plus absorbable poliglecaprone vs. non-absorbable lightweight Prolene}, it was found that the Ultrapro arm did develop erosion, urine retention and de novo urgency [***95****: Okulu et al. Use of three types of synthetic mesh material in sling surgery: A prospective randomized clinical trial evaluating effectiveness and complications. Scandinavian Journal of Urology, 2013; 47: 217–224*]. Milani et al showed a 14.8% exposure rate and a 9% dyspareunia rate with Ultrapro [***96***: *Milani, AL. MEDIUM-TERM CLINICAL OUTCOMES FOLLOWING TROCAR-GUIDED MESH REPAIR OF VAGINAL PROLAPSE USING PARTIALLY ABSORBABLE MESH. Int Urogynecol J (2012) 23 (Suppl 2):S43–S244*]. The Ogah Cochrane review discusses how multifilament meshes have less efficacy and more complications than monofilament meshes [***97***: *Ogah J1, Cody DJ, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. Neurourol Urodyn. 2011 Mar;30(3):284-91*].

Based upon the principles/ characteristics described above (pore size, weave and weight), nonabsorbable synthetic materials have been categorized into four types [***98:*** *Amid, P.K. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia, May 1997, vol 1, issue 1: 15-21*].

- Type I –Macroporous (>75 microns), such as monofilament polypropylene (Prolene, Marlex; Ethicon TVT is a type I mesh). There are not any professional organizations/ associations that agree upon a SPECIFIC mesh weight for UI. Part of this reason is demonstrated in other Ethicon products used for vaginal prolapse repairs. Prolift (polypropylene) & Ultrapro are also highly studied mesh devices, which are lightweight at 45 gm/ m2, 2.5 mm pores & ultra-lightweight at 28 gm/ m2, respectively. Mesh exposure is the same for these non-absorbable and partially absorbable materials, however, as seen with Vypro, the dissolved portion caused local inflammation, higher recurrences and excess contraction [***106***]. It would not work well to use Prolift/ Ultrapro mesh material in TVT or other MUS, just because it is lightweight, as it will probably not be durable. Ethicon conducted a study for the use of Ultrapro in a stress urinary incontinence sling and found this partially absorbable mesh, would not be feasible because it stuck to the sheaths in a cadaveric study [***99****: ETH.MESH.09922570 - TVTO PA (TOPA) RD Memo on PA Mesh Assessments for TVTO-PA - Katrin Elbert Dec 12_2012.pdf*]. If there are only 3 pores across, this is probably not enough support that is required as the backboard of the urethra for urinary continence. Treating an anatomical problem versus a functional problem requires different specifications. Prolift and Ultrapro have not been cleared for SUI treatment. In addition, there is a paucity of studies with the use of Prolift and Ultrapro in the SUI context, compared to the significant amount of research done on TVT PP mesh Again, multifilament meshes have less efficacy and more complications than monofilament meshes as noted in the Ogah Cochrane review of synthetic slings for SUI [***97****: Ogah 2011*].

- Type II –Microporous (<10 microns), such as expanded polytetrafluoroethylene (Gore-Tex).

- Type III –Macroporous (>75 microns) grafts with either microporous components or multifilament fiber structure. Examples include, polyethylene (Mersilene), which is both microporous & multifilament; ObTape, which is microporous polypropylene; and IVS Tunneler, which is multifilament polypropylene. The latter two have been associated with higher rates of infection and erosion [***100:*** *Baessler K, et al. Severe mesh complications following intravaginal slingplasty. Obstet Gynecol. 2005;106(4):713.);*]. OBTape has been removed from the market and IVS Tunneler is not being marketed.

- Type IV –Submicroscopic pore size (polypropylene sheet, Cellgard), which is rarely used in gynecologic surgery.

Steps of allograft processing

The steps involved in processing include harvesting, host cell removal, preservation and sterilization, in order to produce a non-immunogenic graft. Unfortunately, the methods used by companies to process human tissue allograft production varies and the

details are not publicly disclosed. This makes it difficult to develop evidence-based comparisons [***84:*** *Trabuco2013*].

Harvesting

The harvesting of fascia lata and dermis is done aseptically from cadavers. The epidermis is mechanically or chemically separated from the dermis, followed by extraction of the collagen matrix from the dermis [***84:*** *Trabuco2013*].

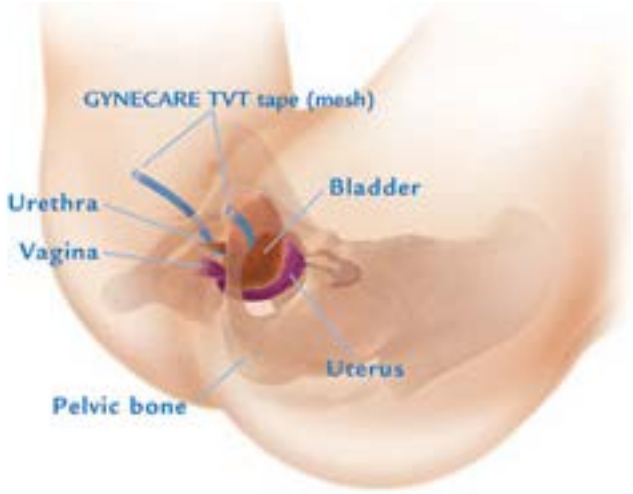
Host cell removal

The host cell is then made acellular by washing it in a solution to extract cell surface proteins (such as, human histocompatibility antigen, HLA) and sugar moieties, in order to achieve a non-immunogenic graft. This is tricky, as solvents must remove cellular debris without permanently denaturing the protein scaffold. The cellular extraction process is imperfect [***101:*** *Fitzgerald MP, Mollenhauer J, Brubaker L. The antigenicity of fascia lata allografts. BJU Int. 2000;86(7):82*], as in one study, the HLA type of allograft donors could still be identified in freeze-dried and Tutoplast processed grafts. Repliform was not conducive with the assay used in the study, thus antigenicity could not be determined. One could argue that not all contaminating DNA had been extracted, but this does not necessarily signify that the grafts were immunogenic, because host rejection is not mediated by DNA or other intracellular components, but rather by host lymphocyte detection of cell surface proteins and sugar components [***84:*** *Trabuco 2013*].

Preservation

The collagen and extracellular matrix must then be preserved and sterilized. Preservation is done via lyophilization (freeze-dried under vacuum) or solvent dehydration [***84:*** *Trabuco 2013*].

Sterilization



Sterilization can be done with gamma irradiation. All of these processing steps appear to affect the final graft strength. In the case of freeze drying, the more ice crystals formed, the weaker the final product and in the case of gamma irradiation, temperature influences the degree of free radical formation. These processes affect the final integrity of the material and, probably, graft performance. However, there are only a few studies which have compared different allografts by preimplantation strength and have not been consistent with reports of clinical performance. In one study, the preimplantation maximum load to failure and stiffness were significantly higher for solvent dehydrated compared with freeze-dried fascia lata [***102:*** *Lemer ML, Chaikin DC. Tissue strength analysis of autologous and cadaveric allografts for the pubovaginal sling. Blaivas JG. Neurourol Urodyn. 1999;18(5):497*]. Yet, solvent dehydrated allografts have consistently been reported to result in early failure after pubovaginal sling [***103:*** *Huang YH, et al. High failure rate using allograft fascia lata in pubovaginal sling surgery for female stress urinary incontinence. Urology. 2001;58(6):943;* ***104:*** *McBride AW, et al. Comparison of long-term outcomes of autologous fascia lata slings with Suspend Tutoplast fascia lata allograft slings for stress incontinence. Am J Obstet Gynecol. 2005;192(5):1677*], sacrocolpopexy [***105:****Culligan PJ, et al. A randomized controlled trial comparing fascia lata and synthetic mesh for sacral colpopexy. Obstet Gynecol. 2005;106(1):29*] and vaginal reinforced repairs] and vaginal reinforced repairs [***106:*** *Gandhi S, et al. A prospective randomized trial using solvent dehydrated fascia lata for the prevention of recurrent anterior vaginal wall prolapse. Am J Obstet Gynecol. 2005;192(5):1649*]. Then in the only study which evaluated vaginal repair with a freeze-dried graft, there was a high failure rate [***107:*** *Ward RM, et al. Vaginal paravaginal repair with an AlloDerm graft: Long-term outcomes. Am J Obstet Gynecol. 2007;197(6):670.el*].

Xenograft processing

When it comes to xenografts, the processing also includes harvesting, host cell removal, preservation and sterilization. Since the processes are usually proprietary, comparisons among different grafts are difficult. A concern is that some patients have had increased tissue reaction with xenografts, leading to questioning as to how well the processes to remove cellular debris truly are. Also, xenografts undergo chemical crosslinking

(such as, Pelvicol), which is one of the key determinants of host response, rendering the graft functionally nonporous. This leads to the absence of host cellular infiltration, causing encapsulation (similar to synthetic type II materials). Non-crosslinked xenografts (such as, Surgisis, Xenform) are marketed as serving as a biologic scaffolding for fibroblast and angioblast ingrowth; and subsequently replaced by host connective tissue [***85*** *Trabuco 2007*]. Although crosslinking is performed to permanently stabilize the material, crosslinked graft resorption over time is still an area of concern, as it is not known whether eventual graft loss affects the structural integrity of the repair.
In other words, as has been noted in long term studies, allografts will eventually fail in the long term and are essentially fully absorbed [***101*** *Fitzgerald 2000*].

HISTORY OF TRANSVAGINAL TAPE (TVT)

How the midurethral position was chosen: the Integral Theory: In 1990, Petros and Ulmsten [***81:*** *Petros 1997*] described the integral theory of female urinary continence, a concept that would become the gold standard modern approach to anti-incontinence surgery and bring in the era of the midurethral sling. The theory proposes that a physiologic 'backboard' is created through fixation of the middle region of the urethra to the pubic bone, via the pubourethral ligaments, and that this factor is critical for the mechanism of continence. Loss of the pubourethral ligament support, or backboard, prevents normal urethral coaptation (urethral tissue union) during times of increased intra-abdominal pressure, resulting in urinary incontinence. The clinical application of this concept was then then demonstrated by repositioning of the sling to a more distal location beneath the urethra than what had previously been used (bladder neck and proximal urethra). This became to be described as the midurethral sling.

Expanding on the integral theory, Ulmsten and Petros [***72:*** *Ulmsten 1995*] first described outcomes of 50 patients after intravaginal sling placement performed via a minimally invasive technique in 1995. In addition to its midurethral anatomic location, another, important modification was implemented by placing the sling in a tensionless fashion, in order to minimize direct urethral pressure. This resulted in re-producing the backboard feature of the integral theory. The original midurethral sling model of Ulmsten and Petros led to the development of tension-free vaginal tape (TVT), which was introduced as a commercially available kit by Gynecare. Several mesh materials—Dacron, Mersilene, Gore-Tex and Marlex-were tried, but were found to have higher rates of erosion and tissue rejection. Prolene polypropylene proved to be the best material, as it allowed tissue integration and a minimal inflammatory response [***72: Ulmsten 1995; 108:*** *Petros, P. Creating a gold standard surgical device: scientific discoveries leading to TVT and beyond: Ulf Ulmsten Memorial Lecture. Int Urogynecol J DOI 10.1007/s00192-015-2639*].

History of TVT, By Dr. A. Arnaud (Medical director for France), 7/2000

In 1995, Dr. Arnaud visited Professor Ulmsten, a Swedish surgeon, in Uppsala. Dr. Arnaud's conclusions after his meeting were as follows:

- good rationale, brilliant idea with many years of serious scientific research
- minimally invasive, should be performed under local in 1/2 hour; relatively easy to perform
- efficiency for short-term cure of SUI demonstrated by having patient cough before and after mesh placement
- efficiency for long-term not yet substantiated, but since mesh used, lead to anticipation of good results long-term.

It was thought even then, to replace the gold standard, i.e. Burch retropubic urethropexy, since BRU required general endotracheal anesthesia, was not easy to perform (especially in a minimally invasive fashion) and had poor long-term results. There were few complications reported by Pr. Ulmsten, probably due to several reasons. First of all, he was a true scientist (a person who engages in seeking knowledge based on demonstrable and reproducible data, by obtaining measurable results through testing and analysis). Science is based on fact, not opinion or preferences. The process of science is designed to challenge ideas through research. Moshe Pritsker, a former post-doctoral researcher at Harvard Medical School, stated: "the reproducibility of published experiments is the foundation of science. No reproducibility – no science."[***109:*** *http://www.livescience.com/20896-science-scientific-method.html*]. Another reason for the low complication rate was that this was a short procedure, there was an external sheath present, and polypropylene was being used.

Polypropylene (PP) material has been around for a long time, for the purpose of augmentation of hernia repairs. Current options for synthetic hernia repair continue to use this mesh material. The modern history of mesh started with Francis Usher's introduction of polypropylene in 1958 [***110:*** *Usher FC, Ochsner J, Tuttle LL. Use of Marlex mesh in the repair of incisional hernias. Am Surg. 1958;24:969-974*]. PP can be woven into a mesh, which is a monofilament, hydrophobic, large-pore mesh that has been one of the primary "work horses" in hernia surgery for the past 50 years. Currently PP comes in a variety of weaves including single strand, double strand, and multifilament. Ramshaw highlighted the recent development of lightweight (LW) PP, which utilizes a lighter PP strand with larger interstices or pores. In the general surgery world, it is compared it to polyester, which was popularized in Europe in 1960 with the Rives-Stoppa technique [***111:*** *Rives J. Surgical treatment of the inguinal hernia with Dacron patch. Int Surg. 1967; 47:360-361*]. Prolene polypropylene mesh is a lightweight, knitted, monofilament, macroporous mesh; however, polyester mesh is a

nonwoven mesh, which is multifilamented and hydrophilic. Expanded polytetrafluoroethylene (ePTFE), is a derivative of Teflon. It was developed in the 1970s and has a proven track record in herniorrhaphy. In contrast to the woven meshes, ePTFE has a microporous, smooth-textured construct that minimizes tissue ingrowth. This is a critical factor in laparoscopic ventral hernia repair, where the mesh is placed in the peritoneal cavity in juxtaposition to the bowel and other viscera [***112:*** *Highlights of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) 2008 Annual Scientific Session and Postgraduate Course*].

TVT launch

In 1997, there was a market launch

1) the device was named TVT

2) a professional video illustrating the procedure was developed

3) clinical studies were begun with RCT comparing TVT and BRU

4) an experts meeting was held in Dublin to include 11 experts from all over Europe

5) a symposium was held during IUGA in Amsterdam, July 1997

In June of 2000, a summit meeting, directed by Dr. Vincent Lucente, took place. At the time, Ethicon had state-of-the-art surgeon and patient teaching materials. The TVT surgeon's monograph of the procedure was presented. At that point, >100,000 Gynecare TVT procedures had been performed. There were 23 clinical papers, involving 1392 patients, showing a cure rate of 89%. At that point in time, it was 5 years of data by Gynecare.

The surgeon's monograph *[**113:** Surgeon's resource monograph. Expert opinions on the use of Gynecare TVT tension-free support for incontinence. A report of the June 2000 Summit Meeting, 17-surgeon panel representing more than 1200 cases*] gave a very detailed explanation of product use, to include how to avoid danger by the exercise of care in the use of the product. It made users aware of the potential dangers inherent in the product and their avoidability.

The following is an outline of the topics covered to address these points:

- preparation
- anesthesia
- abdominal suprapubic and vaginal incisions
- bladder positioning

- detailed written and illustrative description in the placement of the TVT device, along with cystoscopic findings (and including bladder perforation and subsequent readjustment of the TVT)
- antibiotic use
- postop care
- precautions, adverse reactions, contraindications
- complications with causes and recommendations for:
  - vaginal bleeding
  - retropubic hematoma
  - vaginal perforation
  - difficulty placing needle
  - bladder perforation
  - urinary retention
  - urethral injury
  - urethral erosion
  - mesh protrusion
  - vascular injuries
  - bowel perforations
  - de novo void dysfunction
  - mesh infection
  - UTI
  - device failure

The properly trained surgeon, who understands the intricacies of urinary incontinence, should be able to successfully perform the TVT procedure, with a low risk profile for complications.

Studies showed that it worked in various cohorts including SUI, recurrent SUI, ISD and mixed incontinence. The PVS and Burch do not have this utility of being used in these various patient types. TVT works well in all of these various cohorts, thus a very useful product. This utility (along with the many others discussed) of the TVT product, outweighs the risks.

A variety of sling placement techniques have been developed since the TVT device was introduced (top-to-bottom, transobturator inside out, transobturator outside-in, adjustable single-incision slings, etc.) Despite the variety of sling placement techniques, the concept of the midurethral sling has undergone minimal changes since its description by Ulmsten and Petros in 1995. *[**114**: Rapp DE1, Kobashi KC. The evolution of midurethral slings. Nat Clin Pract Urol. 2008 Apr;5(4):194-201*].

TVT MUS continues to make sense because with the multiple, reproducible and scientific studies, the same concept is validated. Just over one year ago, this theory was once again proven at the pelvic floor ultrasound workshop held at the International Uro-Gynecologic Association (IUGA) annual meeting held in Washington, 2014; where trans-

labial/transperineal ultrasonography was shown to determine mobility of the entire urethra. It demonstrated that the mid-urethra, rather than the bladder neck, is what matters most for SUI [***115:*** *IUGA pelvic floor US workshop, Washington, 2014*].

GYNECARE TVT Device Specifications.

The TVT MUS is a monofilament, knitted, macroporous, synthetic mesh sling attached to trocars. The GYNECARE TVT Device is a sterile single use device, consisting of one piece of undyed or blue (Phthalocyanine blue) PROLENE Polypropylene Mesh (tape) approximately 1/2 x 18 inches (1.1 x 45 cm) and approximately 0.027 inches (0.7 mm) thick. It is covered by a plastic sheath, cut and overlapping in the middle and held between two stainless steel needles, bonded to the mesh and sheath with plastic collars [Gynecare TVT IFU]. Ethicon TVT weighs approximately 90–100 gm/ m2 and has a pore size of 1379 microns (well above 75 microns, which is considered a macropore). The GYNECARE TVT Device is available in either mechanical cut or laser-cut versions. The edgeless plastic implant sheath is easily removed to minimize mesh pre-tensioning and distortion.

Content inside the TVT box of this Continence System is:

- trocar
- trocar handle
- trocar shaft
- trocar sheaths and attached Prolene polypropylene mesh
- rigid reusable guide (not included)
- IFU (instructions for use)

The TVT procedure steps for implantation of TVT device are as follows:

- insertion of Foley catheter to drain bladder

- hydrodissection to create space between the vaginal wall and the periurethral fascia

- incision 1.0 cm cephalad from the urethral meatus at the level of the mid urethra

- 0.5 to 1.0 cm paraurethral lateral dissections to accommodate the tips of the Trocar Sheaths

- identify exit points, 2 cm on each side of the midline, immediately above the pubic symphysis (sites chosen to avoid the inferior epigastric vessels)

- retropubic hydrodissection (to open up the retropubic space & further minimize risk of bladder puncture during retropubic trocar passage)
- GYNECARE TVT Reusable Rigid Catheter Guide to displace bladder
- passing of TVT trocar sheath unit through dissected space, while using dominant hand to hold the trocar handle
- placing index finger under the anterior vaginal wall, just lateral of the suburethral incision
- perforating urogenital diaphragm & immediately lowing trocar handle to ensure close contact with the back of the pubic symphysis
- advancing trocar sheath into & through retropubic space
- complete passage and release trocar sheath
- withdraw trocar shaft from within sheath
- displace the bladder to the contralateral side & repeat steps on contralateral side
- perform cystoscopy to assure integrity of bladder
- pull trocar sheaths gently to bring implant loosely under mid urethra
- adjust Implant to patient specifications (only a few drops of leakage upon Valsalva induction)
- cut implant bilaterally and remove sheath, while placing scissors or forceps between urethra and implant
- cut implant just below skin level
- close vaginal and abdominal skin incisions

High volume and high quality studies exist on the TVT MUS, with more than 100 RCTs. It is the most studied mesh device there is. "Irrespective of the routes traversed, mid-urethral slings are highly effective in the short and medium term, and accruing evidence demonstrates their effectiveness in the long term" [***17****: Ford 2015*]. Long term studies of 10 years, demonstrated that the subjective success rates of 77-90% [***116:*** *Groutz A, et al. 10-Year Subjective Outcome Results of the Retropubic Tension-Free Vaginal Tape for Treatment of SUI.*

Journal of Minimally Invasive Gynecology, Vol 18, No 6, November/December 2011; ***117:*** *Heinonen P, et al. Tension-free vaginal tape procedure without preoperative urodynamic examination: Long-term outcome. International Journal of Urology (2012) 19, 1003–1009;* ***118:*** *Serati M, et al. Tension-free Vaginal Tape for the Treatment of Urodynamic Stress Incontinence: Efficacy and Adverse Effects at 10-Year Follow-Up. EUROPEAN UROLOGY 61 (2012) 939–946*]; and objective cure rates of 90-93% [***117:*** *Heinonen 2012;* ***118:*** *Serati 2012*]. Mid-urethral slings have a positive impact on improving the quality of life of women with SUI. 17-year data shows the TVT operation is associated with a high satisfaction and cure rates, and a small risk of complications when performed with the proper technique [***119:*** *Nilsson CG, et al., Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J, 2013. 24(8): p. 1265-9*]. Other long-term data also supports this conclusion [**120**: *Svenningsen R, et al., Long-term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogynecol J, DOI 10.1007/s00192-013-2058-2 (2013);* ***121****.1: Aigmueller T, et al., Reasons for dissatisfaction ten years after TVT procedure. Int Urogynecol J (2014) 25:213-217*].

There are two main ways of carrying out TVT MUS operations, either by inserting a tape behind the pubic bone through the abdomen (’retropubic’ or RPR), or through the groin (’transobturator’ or TOR).

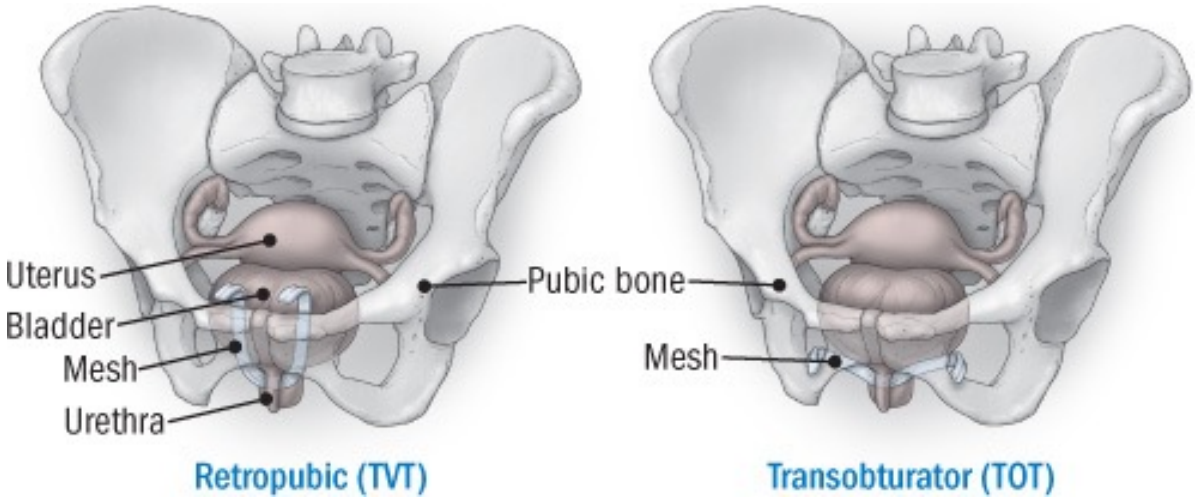


FIGURE 2 TVT: The insert shows the retropubic location with reference to the bony landmarks.

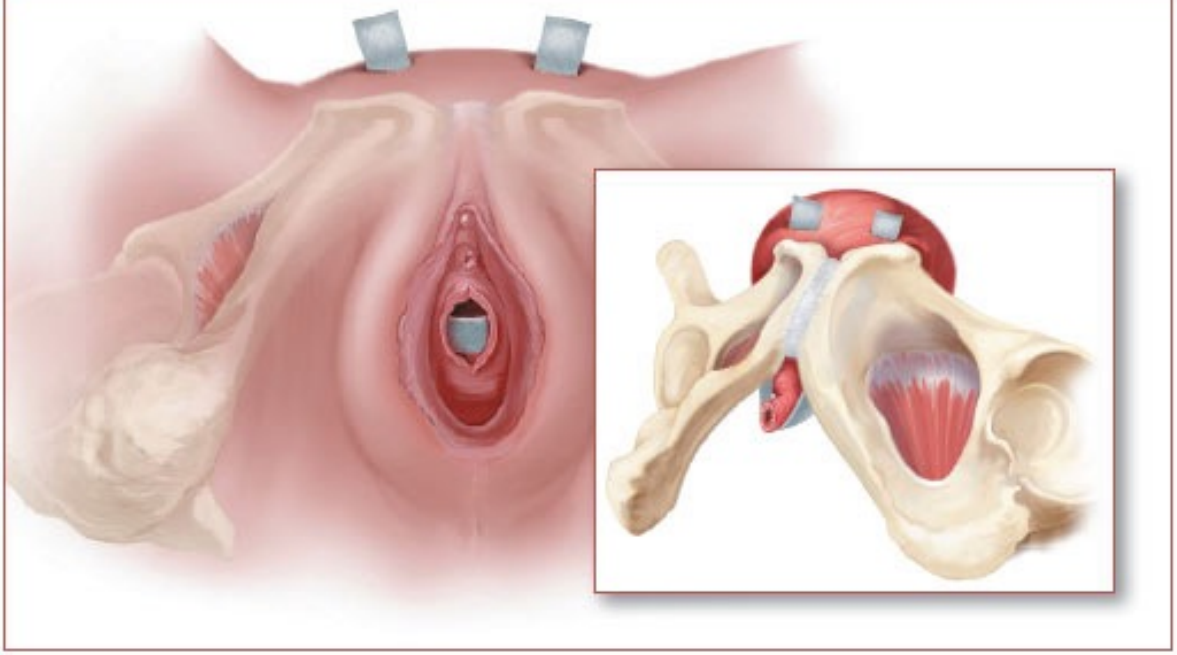
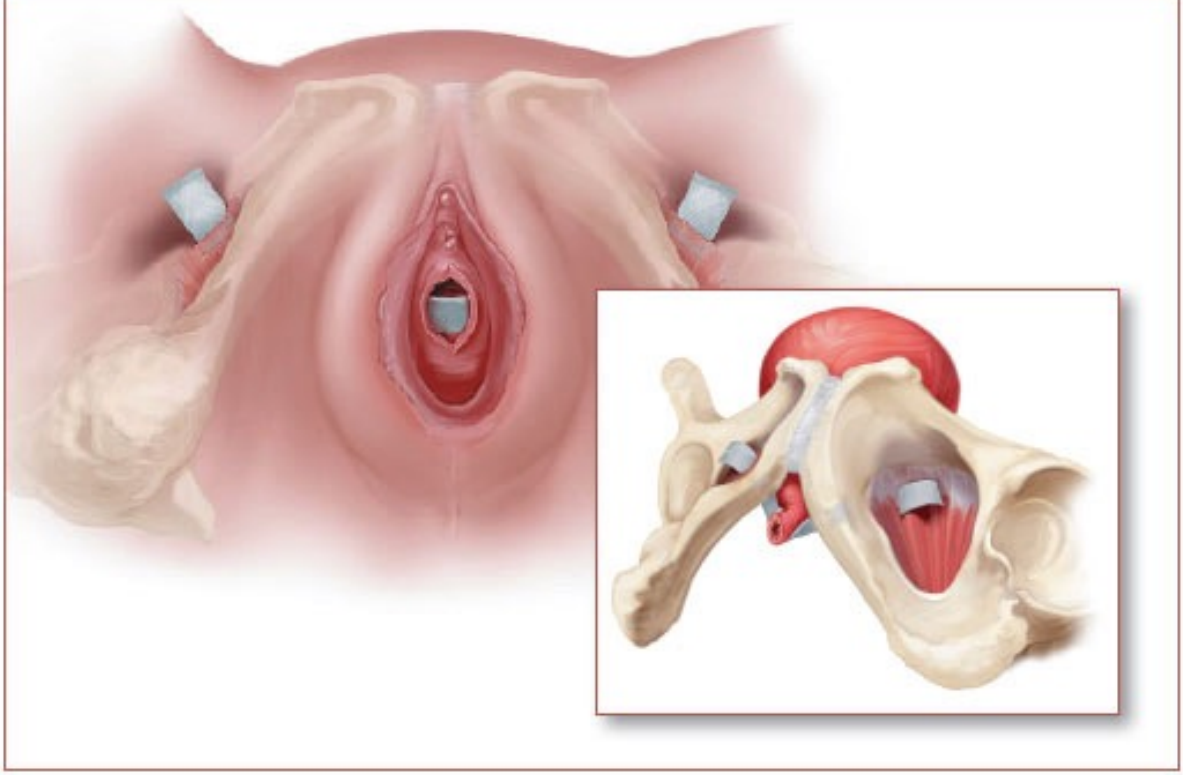


FIGURE 3 TOT: The insert shows the transobturator location with reference to the bony landmarks.



Midurethral slings compare very favorably to other procedures (prior gold standard procedures). In general, midurethral slings are as effective—and often more effective in the long term—as other surgical treatments for SUI; but with a shorter operative duration and a lower risk of certain postoperative complications.

This was demonstrated in a meta-analysis of 62 randomized trials [***121:*** *Ogah J, Cody JD, & Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst. Rev. CD006375 (2009)*].

In terms of short-term (12 month) effectiveness, the subjective cure rate of SUI among women who underwent placement of midurethral slings was comparable to other procedures:

- Midurethral sling versus open retropubic colposuspension (79 versus 82%).
- Midurethral sling versus laparoscopic colposuspension (82 versus 74%).
- Midurethral sling versus bladder neck sling (73 versus 71%).
- Midurethral sling versus autologous fascial bladder neck sling, subjective cure favored midurethral sling in a 2014 meta-analysis of randomized trials [***78:*** *Schimpf* ***2014***].

Long-term (5-year) effectiveness of midurethral slings was comparable as well.

- Midurethral sling versus open colposuspension in one randomized trial (63 versus 70%)
- Midurethral sling versus laparoscopic colposuspension in another randomized trial (92 versus 89%) [***122:*** *Ward KL, Hilton P. Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up. UK and Ireland TVT Trial Group BJOG. 2008;115(2):226 ;****111.1:*** *Jelovsek JE, Barber MD, Karram MM, Walters MD. Randomised trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow up. Paraiso MF BJOG. 2008;115(2):219*].
- Longer-term effectiveness (two prospective cohort studies of 7-11 years) after tension-free vaginal tape procedures (the first midurethral sling that was introduced) reported subjective cure rates of 77 to 85% [***123:*** *Nilsson CG, Palva K, Rezapour M. Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence. Falconer C Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(8):1043;* ***124:*** *Liapis A, Bakas P. Long-term efficacy of tension-free vaginal tape in the management of stress urinary incontinence in women: efficacy at 5- and 7-year follow-up. Creatsas G Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(11):1509*].

The 2009 meta-analysis also revealed:

- The operative duration was significantly shorter for midurethral sling procedures by an average of 71, 15, and 25 minutes compared to bladder neck slings, open colposuspension, and laparoscopic colposuspension, respectively.

- The rate of most perioperative complications was essentially equivocal [***121:*** *Ogah 2009*]. The primary exception was perforation of the bladder or rarely urethra [***125:*** *Morton HC. Urethral injury associated with minimally invasive mid-urethral sling procedures for the treatment of stress urinary incontinence: a case series and systematic literature search. Hilton P BJOG. 2009;116(8):1120*], which occurred more frequently during midurethral sling surgery compared with open or laparoscopic colposuspension (4.7 versus 1.1% and 4.9 versus 1.7%). Bladder perforations associated with midurethral slings add little to patient recovery time (they are managed with a bladder catheter for a few days) [***126.:*** *Crosby EC, Vilasagar S, Duecy EE. Expectant management of cystotomy at the time of midurethral sling placement: a retrospective case series. Flynn MK Int Urogynecol J. 2013 Sep;24(9):1543-6. Epub 2013 Feb 16*]; and do not appear to have serious sequelae or affect SUI cure rates, thus should not impact the choice of procedure for this particular finding [***127:*** *Gold RS, Groutz A, Pauzner D, Lessing J. Bladder perforation during tension-free vaginal tape surgery: does it matter? Gordon D J Reprod Med. 2007;52(7):616*].
- Adverse effects on bladder function occurred with less or similar frequency in women who underwent midurethral sling procedures. De novo urinary urgency or urgency incontinence was significantly less frequent with MUS than bladder neck slings and laparoscopic colposuspension (6 versus 17% and 4 versus 13%), but not open colposuspension (9 versus 12%).

- The rate of voiding dysfunction (such as incomplete bladder emptying or urinary retention) following midurethral sling surgery did not differ significantly from bladder neck slings (10 versus 13%), open colposuspension (6 versus 9%), or laparoscopic colposuspension (4 versus 6%) [***121*** *Ogah 2009*]. More recently, in a small study from Denmark, 94% of patients who developed VD, were relieved while still maintaining continence, if a tape mobilization through the vaginal incision was performed at approximately 2 weeks postoperatively.

- Hospital stay was significantly shorter for midurethral slings compared with bladder neck slings (0.5 days shorter), open colposuspension (four days), and laparoscopic colposuspension (one day).

- Return to normal activity for MUS compared with laparoscopic colposuspension was six days shorter.

- Midurethral slings appear to be more cost-effective than other procedures [***128:*** *Kilonzo M, et al. Cost effectiveness of tension-free vaginal tape for the surgical management of female*

stress incontinence. McCormack K Int J Technol Assess Health Care. 2004;20(4):455; ***129:*** *Cody J, et al. Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence. Grant A Health Technol Assess. 2003;7(21):iii*].

- In addition, it is evident that women undergoing MUS had a significantly reduced risk of re-operation for UI when compared to abdominal retropubic surgery [***130*** *Abdel-Fattah, A Familusi, S Filding, J Ford, S Bhattacharya. Primary and repeat surgical treatment for female pelvic organ prolapse and incontinence in porous women in the UK: a register linkage study. BMJ 2011: 1-10*].

In summary, midurethral slings have comparable efficacy to other procedures, but a shorter operative duration and recovery time. While most complication rates are similar across procedures, midurethral slings have a lower rate of de novo urinary urgency symptoms. The main disadvantage of midurethral slings is the risk of bladder perforation, but this complication is easily managed. Thus, midurethral sling placement is the surgical treatment of choice for most healthy women with SUI who desire surgical treatment [***131:*** *J Eric Jelovsek, Jhansi Reddy, MD. Surgical management of stress urinary incontinence in women: Choosing a primary surgical procedure. uptodate.com Literature review current through: Jul 2015*].

Women with apical prolapse are possibly an exception to this general conclusion. Thus, for women who are undergoing open abdominal sacrocolpopexy (ASC), one might argue that a Burch retropubic urethropexy rather than midurethral sling placement, might be a better option, since the patient is already "open." However, the BRU is still less efficacious and performing it, adds additional time and exposure of the "open" abdomen to possible infection, as well as bleeding.

In addition, the TVT has been shown to also be effective when concomitant prolapse surgery is being performed, including apical prolapse procedures, such as ASC.

DESIGN OF THE TVT DEVICE

I. The usefulness and desirability of the product.

Ethicon's studies of the TVT from its inception, have allowed other researchers and surgeons to study it as well, because it has been made reproducible and the surgeons/researchers know what they are obtaining.

The design of the TVT is universally accepted by the large academic bodies: ACOG, AUGS, AUA, EUA, ICS, IUGA, NICE and SUFU. In a recent study involving 53 expert urologists and urogynecologists and who could select among many surgical options, the full-length synthetic midurethral sling was the preferred option in 93% for the surgical treatment of primary stress incontinence [***132****:Nager, C.W., et al., A randomized trial of urodynamic testing before stress-incontinence surgery. N Engl J Med, 2012. 366(21): p. 1987-97*] *(AUGS position statement, 2013*]. This procedure is probably the most important advancement in the

treatment of stress urinary incontinence in the last 50 years and has the full support of organizations which are dedicated to improving the lives of women with urinary incontinence. These professional and academic organizations agree that it is less morbid than many other prior procedures [***133****:AUGS position statement on restriction of surgical options for PFD, 2013*]. The design of the TVT makes sense to the pelvic surgeon, as the TVT is placed in an area of the pelvis that the surgeon is an expert in operating upon, and has a physiologic-scientific basis. This is supported by the fact that it is placed in the mid-urethral position, the site that most frequently is known to develop weakness, which has a vitally important function in the maintenance of continence. In addition, to the public and to the patient, the design also makes sense. Ethicon has excellent patient information hand-outs that make the procedure understandable to the "lay person" [***134 ETH.MESH.08003173-80; ETH.MESH.08003263-78;ETH.MESH.08003303-18***].

The most up-to-date Cochrane review, published in May of 2015 [***17:*** *Ford 2015*], illustrates that mid-urethral slings have a positive impact on improving the quality of life of women with stress urinary incontinence [***121:*** *Ogah 2009*], thus validating the desirability to the public and more importantly, the patient.

Cochrane is a well-regarded entity that provides high-quality information for which to base health care decisions upon. A Cochrane review is a systematic review that attempts to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question. Researchers conducting systematic reviews use explicit methods aimed at minimizing bias, in order to produce more reliable findings that can be used to inform decision making.

Another study validating patient desirability to the MUS was on sexual activity and function, which was assessed in 597 women with stress urinary incontinence. These women were enrolled in a randomized equivalence trial of retropubic compared with transobturator midurethral slings. It was found that midurethral sling surgery for stress urinary incontinence significantly improved sexual function [***135****: Zyczynski HM, et al. Sexual activity and function in women more than 2 years after midurethral sling placement: AJOG Nov 2012*]. In the May 2015 Cochrane review, the authors found that leakage of urine during intercourse was improved following insertion of these tapes [***121:*** *Ogah 2009*].

All of the data presented thus far (with more discussed below), further exemplifies the utility of the device as being very high, which is critically important. The utility of the TVT has been demonstrated in its ease of use, low morbidity, reproducibility, adaptability and efficacy. The procedure is reproducible by pelvic surgeons, can be done under multiple anesthesia modes (including general, regional and even local anesthesia), as well as a "stand alone" procedure or in conjunction with other surgical procedures. This is the most studied medical device.

Further utility and desirability factors are delineated below:

- During the peri-operative period: as it is an outpatient approximately 30-minute procedure, it involves tiny incisions, it can be done using only local anesthetic if desired, the patient's continence can be tested during the procedure, discharge typically occurs within 3-4 hours of completion of the procedure, most patients do not need to go home with a Foley catheter, most women can drive a car the day after the procedure, most women can resume working within 2 days and return to normal, non-strenuous exercise in just 1 week, the procedure involves little pain (with many patients not even needing narcotic pain medications).

- The device requires a very small upper passage on the suprapubic skin, which can be sealed with dermabond or a stitch.

  The TVT is easy to place, thus making it accessible to more surgeons around the country, and thus more women.

- The TVT mesh is made of a material that is well-known in the surgical field. Prolene has been used for over 50 years in various applications, it has been shown to work in various applications and exhibit a well-established and known reaction in the body, Desirability to have a base material that is known in the field. The mesh is not carcinogenic, and I am unaware of any reported cases of malignancy in humans due to the implantation of surgical grade polypropylene for MUS. There has been 0% malignancy after polypropylene mesh MUS were used in 2545 cases performed from 2004-13 [***136:*** *Moalli P, et al. Polypropylene mesh: evidence for lack of carcinogenicity. Int Urogynecol J. Mar 2014.125 King AB, Goldman H. Current Controversies Regarding Oncologic Risk Associated with Polypropylene MUS. Current Urol Rep, 2014 (15): 453. 126 King AB, Zampini A, Vasavada S, Moore C, Rackley R, Goldman H. Female Urology Jul 2014: 789-92*].

- The synthetic mesh used in the TVT is not met with cultural or religious objections like xenografts or allografts.

- The mesh used in the TVT is state of the art in design. It is macroporous (>75 microns) and monofilament, and the macroporosity for an only 1.1-cm-wide strip of mesh promotes mechanical anchorage with neovascularization and collagen formation [***98****: Amid 1997*].

- The TVT is useful in multiple different patient cohorts. It is safe and effective when used in old patients and young patients, pre- and post-menopausal patients, patients with primary or recurrent SUI, and patients with SUI or mixed incontinence.

- The majority of patients who have SUI and OAB symptoms have a reduction of OAB symptoms following implantation of the TVT device.

- The TVT is less invasive than traditional surgical treatment options like pubovaginal slings or the Burch procedure. The patient can have a totally vaginal surgery rather than having an abdominal component to the surgery, and implantation of the device involves small incisions. This makes sense, as the urethra is readily accessible to the surgeon, in the area of the anterior vaginal wall. A comparable from more-invasive abdominal surgeries to less-invasive vaginal surgeries also has occurred over the years, as seen in in hysterectomy surgery.

- The width of the mesh is only 1.1 cm (with the average overall length of the urethra is 3-4 cm), yet it is wide enough to support the midurethra.

- The TVT follows the Integral theory (explained previously). Ulmsten studied and found midurethra provides best location to support urethra [***81****: Petros 1997*].

- The TVT, unlike prior SUI treatments, is anchorless. Prior anchored treatments led to pain, voiding problems, and anchor point problems, such as Protegen (the FDA's 1999 enforcement report cited the reason for the recall as a "higher than expected rate of vaginal erosion and dehiscence" and noted that the product "does not appear to function as intended).

- The design of the sheaths that cover the TVT mesh during implantation allows for smooth placement. The sheathes carry the load of passage and avoid any distortion of the mesh, they protect the mesh during placement and prevent any detensioning of the sling, they reduce the risk of infection, they allow the placement of the sling to be optimized, they allow for repositioning the tape prior to sheath removal, the sheathes are removable and they are non-reactive.

- Implantation of the TVT is easy to teach and to learn, and is taught in all urogynecology programs. Female urologists, gynecologists and urogynecologists (or female pelvic medicine and reconstructive surgeons) are expected to be competent to perform per residency and fellowship curriculum, as well as Board Certifications. Based upon the FPMRS program requirements, fellows are expected to know the anatomy and physiology of the pelvic floor, lower urinary tract and vaginal function; along with the diagnosis, evaluation and treatment, using behavioral, pharmacological, functional and surgical treatment of urinary incontinence, micturition disorders, pelvic floor dysfunction and pelvic organ prolapse. More specifically, fellows must demonstrate competence in performing surgery for urinary incontinence including native tissue, synthetic slings and periurethral bulking agents [***137 :*** *Novara, G., et al. Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol, 2010. 58(2): p. 218-38*].

- The TVT provides the ability to have a SUI surgery that can treat the large number of SUI cases that develop each year and have medical indications for surgery.

- The TVT is packaged in such a way that it is sterilized, it has a good shelf life, maintains its integrity during transport and storage, and is designed to include instructions for use, something other surgical procedures like the Burch procedure or fascial slings do not have; and which informs surgeons of professional education. The packaging also includes information that enables the device to be tracked for overall safety analyses and adverse event reporting.

II. The Safety of the Device

As already mentioned, the desirability of the TVT is high, as there are many benefits to women. Along with the outcome benefits, it is safe, with the likelihood of injury and the probability of seriousness of injury being very low. Complications can occur with all types of UI surgeries. For example, with the pubovaginal fascial sling (PFS), there is a high risk for voiding dysfunction and urinary retention, which is difficult to treat and can require a complete removal of the sling, resulting in the original symptoms of UI. These potential complications, should they occur after a TVT, are usually very easily treated. This can include a simple transection of the sling without having to excise a portion or much less likely, the entire sling. And more importantly, without losing the efficacy of the original purpose for placing it; i.e., for the treatment of SUI *[**131:** Jelovsek 2015*].

There is not a single "risk-free surgery" that also has very good efficacy. All surgeries have potential risks and complications. Mesh exposure, although essentially a unique complication to mesh procedures, also has a low risk of occurrence and most exposures are also easily treated with topical estrogen or even in-office simple excision under local anesthesia. This again, would be without losing its efficacy [***131:** Jelovsek 2015*].

The FDA conducted a review of Medical Device Reports (MDRs) during a 3-year period (2005 – 2007), which was reported to be "over 1,000." Since then, from Jan. 01, 2008 through Dec. 31, 2010, the FDA received 2,874 additional reports of complications associated with surgical mesh devices used to repair POP and SUI, with 1,503 reports associated with POP repairs and 1,371 associated with SUI repairs. MUS "have a good safety profile"[***17:** Ford 2015*]. MUS have "low rates of complications" [***97:** Ogah 2011*].

Complication rates are very comparable to—and often more favorable than—BRU and PFS [***78:** Schmipf 2014*]. Dr. Cox in her study of 2013 called the synthetic MUS the "new gold standard first line surgical treatment for women with SUI" [***10***: *Cox 2013*]. In Tommaselli 2015 study, it was noted that 13 patients receiving a retropubic MUS out of 3,974 total patients had persistent or chronic pain, which, if you do the calculation, shows a chronic pain rate of 0.3% [***138:** Tommaselli, et al. Medium & Long term outcomes after MUS for SUI,; systematic review & meta-analysis: The International Urogynecological Journal, May 2015*]. The

most common complications reported through MDRs for surgical mesh slings for SUI repair include: pain, mesh erosion through the vagina (also called exposure, extrusion, or protrusion), infection, urinary problems, recurrent incontinence, pain during sexual intercourse (dyspareunia), bleeding, organ perforation, neuro-muscular problems and vaginal scarring; which may require additional medical intervention, and occasionally, surgical treatment and/or hospitalization. With the exception of mesh erosion, the above complications can occur following a non-mesh surgical repair for SUI as well.

The one unique mesh complication mentioned above may not be so unique after all. Although BRU and PFS are not done with the use synthetic mesh, they are done with permanent synthetic sutures that can also become exposed and erode into the bladder and/or cause pain [***67:*** *Brubaker 2012****; 76:*** *Chai 2009*]. In addition, there is more morbidity as additional incisions are required for both of those procedures, whether it be an abdominal incision for the BRU and PFS, or even two incisions (of the abdomen and thigh) with the PFS. This then carries the additional pain, infection and longer recovery period with it.

Other safety factors that were integrated into the design of the TVT include the following:

- The design of the TVT optimizes safety by using a single, very small vaginal incision about 1.5 to 2 cm, and avoiding the large abdominal incision needed for the BRU and AFS procedures. The Burch procedure, on the other hand, involves a 5-6 inch abdominal incision and a pubovaginal fascial sling that has multiple incisions (a large abdominal incision as well as a vaginal incision to pull the sling up into place). If fascia lata is used rather than rectus fascia, another incision in the leg is needed to harvest the fascia lata.

- The TVT's trocars curve outward and have a blunter tip so that they pass through tissues smoothly. These trocars are quite similar to the instruments used in the PFS, i.e. Stamey needles.

- Passage through retropubic space has been done for more than 50 years. Pelvic surgeons know the organs and anatomy. Thus, although the TVT procedure involves a "blind passage," the anatomy is known and consistent. Doing the procedure as described, maintains its minimal invasiveness and reduction in morbidity. There are multiple procedures that have a "blind passage" step, but are considered safe, as long as the surgical principles are followed. One such example, is placement of the Veress needle in laparoscopic and robotic procedures.

- Bladder injury occurs in very few patients (3%), and can occur with the placement of one of the thin trocars. When recognized, the trocar is withdrawn and placed slightly more laterally, leaving a small (4 mm) puncture hole in the bladder which heals quickly and completely. In most cases, no direct treatment is needed. This is not

unique to the TVT, as noted in BRU, bladder perforation can occur up to 3% of the time [***77**: Appell 2012*].

- Dyspareunia is rare following implantation of the TVT. The design of the TVT places the mesh under the midurethra via the small proximal anterior wall incision. It is located at a part of the vaginal wall, where forces and stress from penile contact are minimal. In addition, the design of TVT then provides for the mesh sling to traverse up (vertically) and away from the vagina.

- Exposures following TVT placement are uncommon and manageable, occurring in about 1-3% of patients. This is typically the result of a breakdown or opening of the vaginal incision after surgery. In most cases, the vagina can be reclosed over the mesh. However in some cases, the exposed portion of mesh is excised and the vaginal tissue closed, which is usually performed as an outpatient procedure under local analgesia and light sedation. Wound dehiscence can also occur in BRU and PFS surgeries.

- Unlike slings made from allografts or xenografts, graft processing is unnecessary. The TVT's synthetic mesh avoids rejection as can occur with allografts and xenografts, avoids the issue of limited availability of allograft tissue, lacks the potential infectious disease transmission, avoids the risk of virus and prion transmission with allograft and xenografts, and avoids the high rate of degradation seen in allografts and xenografts, as these materials have to be irradiated or treated, due to hepatitis B and C, HIV and HTLV-1.

- The macroporous mesh is state of the art, being >75 microns and monofilament. The Amid study of 1997 showed that this macroporosity allows for entry of fibroblasts, macrophages, blood vessels and collagen fibers, for tissue generation and reduction in the risk of infection [***98:** Amid 1997*].

A broad evidence base, including high-quality scientific papers in medical journals in the U.S. and the world supports the use of the MUS as a treatment for SUI. There is robust evidence [***121**: Ogah 2009; **122:** Ward 2008**;**, **137**: Novara 2010*] to support the use of MUS from over 2,000 publications making this treatment the most extensively reviewed and evaluated procedure for female stress urinary incontinence now in use. These scientific publications studied all types of patients, including those with co-morbidities such as prolapse, obesity, and other types of bladder dysfunction. It is, however, acknowledged that any operation can cause complications. For MUS, these include bleeding, damage to the bladder and bowel, voiding difficulty, tape exposure and pelvic pain; all of these may require repeat surgery, but this is uncommon. Nevertheless, the results of a recent large multi-center trials [***140:** Richter H E, et al. Retropubic versus transobturator midurethral slings for stress incontinence. N. Engl. J. Med. 362, 2066–2076 (2010)*] have confirmed excellent outcomes and a low rates of complications to be expected after treatment with MUS. Additionally, long term effectiveness of up to 80% has been demonstrated in studies including one

which has followed up a small group of patients for 17 years. [***123:*** *Nilsson 2008*]. There is not another product that has this degree of efficacy with a low morbidity profile. The following is the most recent long-term review that validates this statement, followed by well-done reviews of study after study repeatedly supporting the MUS.

Randomized or quasi-randomized controlled trials amongst women with SUI, USI, or MUI were identified through a medical literature search up to June of 2014. 81 trials were found, which had a total of 12,113 women, of which both trial arms involved a MUS operation. This Cochrane review was published in May 2015 [***121:*** *Ogah 2009*].

The success of these operations was very good, showing that over 80% of women with stress urinary incontinence were cured, or had significant improvement in their symptoms, for up to five years after surgery. This occurred irrespective of the tapes used or the route of tape insertion. In up to one year postoperatively (i.e., short term), the rate of subjective cure of TOR and RPR was similar at 62% to 98% in the TOR group, and 71% to 97% in the RPR group. Short-term objective cure was also similar in both groups. In up to five (5) years postoperatively (i.e., long term), the rate of subjective cure was 43% to 92% in the TOR group, and 51% to 88% in the RPR group [***121:*** *Ogah 2009*].

In terms of risks and complications, overall reported rates of tape-related complications are low. The retropubic mode versus the transobturator mode of insertion carried a greater risk bladder injury (0.6% versus 4.5%) and postoperative incomplete bladder emptying. However, the retropubic mode led to less groin pain (1.3% versus 6.4%), but slightly higher suprapubic pain (2.9% versus 0.9%); both being of short duration. In addition, there were fewer re-operative procedures in the retropubic route, than the transobturator route. The risk of erosion of the tape into the vagina for both routes of tape insertion was only at 2%. The reported occurrence of problems with sexual intercourse including pain was low, and leakage of urine during intercourse was improved following insertion of these tapes. These last two points were based upon moderate quality evidence. Major vascular/visceral injury, mean operating time, operative blood loss and length of hospital stay were somewhat lower with TOR, but very low overall for both routes [***110***]. There is much less data on transobturator versus transvaginal slings.

There is a lot of data on the MUS, of which long-term outcomes have been reported favorably, in well-designed studies. The following data was found from a systematic review & meta-analysis, on the medium- and long-term outcomes after MUS for SUI, presented in May of 2015.

There were 11 RCTs and 38 nonrandomized studies, including prospective, retrospective, and cohort studies with a total of 6,406 patients (1,200 in RCTs and 5,206 in nonrandomized studies) aged 19 – 89 years [***138:*** *Tommaselli 2015*]. This meta-analysis indicated that both RP-MUS and TO-MUS are associated with high objective and subjective cure rates in the long-term and medium-term. RCTs showed a significantly higher

subjective cure rate with RP-MUS than with TO-MUS. Non-RCT studies showed a somewhat lower subjective cure rate than objective cure rates for RP-MUS vs TO-MUS (72.7 % vs. 83.2 %). There was no difference between objective and subjective cure rates of TO-MUS in non-RCT studies. The most frequent complication was de novo OAB symptoms for both approaches which, can be treated either with tape division or anticholinergic drugs. The second most frequent complication with TO-MUS was pain, with an incidence of 6%; most were postoperative or persistent pain that resolved within weeks or months, with no long-term sequelae. The rate of chronic pain in the groin and/or the thigh is far lower. RP-MUS showed a higher rate of bladder perforations. The higher incidence of vaginal extrusion with TO-MUS than with RP-MUS was not found in those studies evaluating short-term follow-up. TVT-O was associated with a significantly lower incidence of vaginal injuries than TOT, but other complications did not differ between the two approaches. Overall, these results seem to indicate that both TOT approaches yield similar medium-term safety outcomes [***138:*** *Tommaselli*].

A systematic review was performed of RCTs from Jan, 1990 through April, 2013 comparing a sling for SUI to another sling or BRU, with at least 12 months of follow-up [***80***]. For women considering pubovaginal sling vs Burch, the evidence favored slings for both subjective and objective cure; with the experts recommending pubovaginal sling to maximize cure outcomes. For pubovaginal slings vs MUS, metaanalysis of subjective cure favored MUS. For obturator slings vs retropubic MUS, meta-analyses for both objective and subjective cure favored retropubic slings; metaanalysis showed overactive bladder symptoms were more common following retropubic slings. For mini-slings vs full-length MUS, meta-analyses of objective and subjective cure both significantly favored full-length slings [***80***].

A 5-year RCT comparing RP and TO MUS for SUI, studied a total of 268 women. The objective cure rate was 84.7% in the TVT group and 86.2% in the TVT-O group, with no statistical difference between the groups. Subjective treatment satisfaction was 94.2% in the TVT group and 91.7% in the TVT-O group, with no difference between groups. Complication rates were low, with no difference between groups [***141:*** *Laurikainen et al. Five-year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence; European Association of Urology; Jan 2014.*].

Women are up and about quickly after MUS surgery, returning to their daily routines of family and work, in a much shorter time than with prior gold standard procedures for SUI. The Burch retropubic urethropexy (BRU) and pubovaginal fascial sling (PFS) require a longer recovery period, with the former having a much lower efficacy rate. As mentioned before, modifications to the original TVT that have been made, however, have not proven to be more efficacious. In a 2-year observational study, single-incision sling (SIS), Minitape, 60 women were studied in two tertiary referral urogynecology units in England, and it was found that although feasible to perform, there was a significantly lower cure rate than the TVT (of which 7000 TVT procedures were being done annually

in England). Only 1/2 remained cured at one year, with a rapid decline at 2 years; vs the TVT that has a cure rate of over 90% at 1-2 years. There were not major complications with the minitape, such as bladder, visceral or vascular injuries; however, there were 7 mesh exposures and 5 had pain, with subsequent removal [***142:*** *North, et. al; A 2 year observational study to determine the efficacy of a novel single incision sling procedure (Minitape) for female stress urinary incontinence; BJOG 2010; 117: 356-360*].

Substitute products previously or currently available are not optimal, as noted below:

- Other trocars have larger, pointed tips, with a greater risk of vessel or organ perforation. However, even small, thin trocars have a risk of perforation, due to the fact that tactile feedback is reduced, making organ perforation somewhat more likely, especially in less-experienced hands.

- Many prior slings have not had, or do not have protective sheaths. This can lead to the "dragging effect" and possible tissue trauma. In addition, without the protective sheaths, there is a risk of too much stretching of the mesh, leading to suboptimal efficacy and/or too much tension.

- Other negative factors noted in UI materials is the multifilament factor in the mesh that can subsequently lead to an increased risk of infection and has been shown to have poor tolerability in the pelvic space, thus no longer considered state of the art.

- TVT mesh is macroporous, allowing for collagen and inflammatory cells to enter for the purposes of neovascularization and as a protective mechanism. Microporous mesh, will not allow for WBCs to enter and assist in fighting infection, while allowing only the smaller sized bacteria to enter.

- I disagree with the contention some plaintiffs' experts have made that the polypropylene TVT mesh is carcinogenic. I've never seen cancer from a TVT sling in my practice, and the literature does not support that. An epidemiologic study by the International Agency for Research on Cancer (IARC) in 2000 concluded that there was no evidence for tumorigenicity of metallic or synthetic implants in humans. Over 3 million polypropylene midurethral slings have been sold since the mid-1990s and hundreds of thousands of transvaginal mesh units have been sold in the last 10 years. To date, no mesh site cancers have been reported. [*Moalli, et al. Polypropylene mesh_ evidence for lack of carcinogenicity Int Urogynecol J, 2014-2343-8*]. From 2004-2013, over 2500 procedures were performed, of which 96.3% underwent polypropylene midurethral sling placement, with an average follow-up after sling placement was 42 months. The rate of bladder cancer after the sling procedure was 1 of 2361 (0.0%), with the same rate of vaginal cancer and no sarcomas were noted [*King, Goldman - Is there an association between polypropylene midurethral slings and malignancy, UROLOGY 84 (4), 2014: 789-92*].

"It is known that tumor formation related to biomaterials in animals is largely dependent on the physical, not the chemical configuration of the implant, with smooth large surface areas (discs and thin sheets) being potentially carcinogenic, and irregular disrupted surfaces (e.g. those that contain pores as in meshes) lacking carcinogenicity." [*AUGS-SUFU FAQs by Providers on Mid-urethral Slings for SUI; Ratner, B.D., et al., eds. Biomaterials Science: An Introduction to Materials in Medicine - 3rd Edition. 2013, Academic Press: Waltham, MA; Oppenheimer, B.S., et al., The latent period in carcinogenesis by plastics in rats and its relation to the presarcomatous stage. Cancer, 1958. 11(1): p. 204-13].*

 TVT does already have a low risk of mesh exposure and erosion, but this is a risk in any surgery involving an implant. TVT is offered in laser cut, as well as mechanical cut versions. Either cut is adequate, as there has not been any difference in clinical and physiological responses. Preclinical testing done demonstrated no difference in physiological range. In the physiologic range at which the meshes are exposed during periods of high stress, approximately up to 50 gm/ 0.05 kg (or 0.5 Newtons), the elongation properties of the laser cut mesh and the mechanical cut mesh have been shown to be the same [***143:** Lin, AT,. et al. In vivo Tension sustained by fascial sling in pubovaginal sling surgery for female stress urinary incontinence. Journal of Urology, March 2005*]. In addition, the elongation analysis determined that each of the two methods of cutting produces meshes which have statistically the same properties of elongation within approximately the first 5% elongation of the mesh [***144:** 2006 Mar 3 Flatow memo - CPC-2006-0165 Performance evaluation of TVT PROLENE blue Mesh_ Elongation Properties of Mechanical Cut verses Laser Cut.*]. Some expert witnesses retained by plaintiffs in litigation may argue that mechanical cut mesh leads to fraying and loss of particles leading to pain. However, this has not been shown to occur. I have not seen any literature that discusses particle loss leading to pain, nor have I seen it in my practice.

 In addition, other meshes that have larger pores or even lighter weights than the TVT mesh have not been FDA cleared for SUI treatment. The vast majority of the sling meshes on market for SUI now are monofilament PP, which is considered state of the art, by the large majority of female pelvic surgeons.

 Additionally, the TVT is very aesthetic, with very small incisions that are well hidden.

 The literature reveals few experimental studies on mixed mesh materials such as Vypro mesh (semi-absorbable multifilament; non-absorbable PP plus absorbable polyglactin [vicryl]) and Ultrapro mesh (semi-absorbable monofilament; non-absorbable polypropylene plus absorbable poliglecaprone [monocryl]) [***5:** Yip 2007**; 9:** Dubeau 2006*]. In animal studies, it has been shown that the tensile force increases with time and tissue integration occurs more frequently with Ultrapro mesh [***5:** Yip 2007*]. Only one clinical study exists in the literature on the use of semi-absorbable mixed meshes in sling surgery. In one clinical study involving 144 patients, the incidence of urethral and

> vaginal extrusions following Ultrapro mesh in a synthetic sling procedure different from the TVT procedure, appeared to be lower than that with other synthetic slings in a 4-year follow-up. Ultrapro mesh, demonstrated high success rates, with low vaginal and urethral extrusion, as well as lower de novo urgency rates in clinical use. However, all three arms (including the Ultrapro arm), experienced erosion, retention and de novo urgency [***95:*** *Okulu 2013*]. To my knowledge, however, Ultrapro hasn't been cleared for the use in SUI surgery. This data is not very good as there are now more recurrences, with higher exposure and dyspareunia rates of 14.8 % & 9%, respectively [***Milani***]. The Ogah Cochrane review notes that "macroporous monofilament sling materials have a better balance of efficacy and adverse reactions when compared to multifilament microporous slings." [***114***]. The data does not come close to the long term data of 17 years that we have on the TVT. In addition, when Ultrapro was tested as a sling, it was found to stick to sheathes [***145***: *ETH.MESH.09922570*]**.**

"The polypropylene midurethral sling has helped millions of women with SUI regain control of their lives by undergoing a simple outpatient procedure that allows them to return to daily life very quickly. With its acknowledged safety and efficacy, it has created an environment for a much larger number of women to have access to treatment. In the past, concerns over failure, invasiveness of surgery, and cost, caused a large percentage of incontinent women to live without treatment. One of the unintended consequences of this polypropylene mesh controversy, has been to keep women from receiving any treatment for SUI. This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence" [***146:*** *AUGS-SUFU position statement on MUS for SUI, Jan 2014*].

The TVT has been standardized and compared across all studies. The design factors have shown it to be a very reasonable procedure and as the standard of care for which pelvic surgeons expect. If one were to compare the data that we have on prior gold standards for stress urinary incontinence, including the BRU, AFS or even other procedures, such as the SPARC (another MUS), the amount of data that the TVT has, would far surpasses any of those procedures. There are over 100 RCTs on TVT. There are over 50 studies that have over 5 years duration data on the TVT [***17:*** *Ford 2014;* ***78:*** *Schimpf;* ***79:*** *Broussard 2013;* ***121:*** *Ogah 2009;* ***137:*** *Novara 2010*]. If TVT is considered the standard of care in terms of randomized controlled trials, then there would be no other procedure that would come close. Traditionally, most surgeons perform the procedures that they have been taught through residency and/or fellowships. A surgeon cannot just sit around and not do any procedures, while allowing for 20 years of data to be collected. Surgeons were performing BRU for decades before the first RCT was done. 1996 was the 1st meta-analysis done on the BRU, showing that the quality of data was relatively poor, thus one could not make well informed treatment recommendations as to the best clinical practice, based on scientific evidence. In addition, well documented complications were not well known [***139*** *Black N.A, Downs SH. The effectiveness of surgery for stress incontinence in women: a sys-*

tematic review. British Journal of Urology 1996; 78: 497-510]. In terms of the PFS, it was nearly 80 years after the first one was performed before a RCT had been done (PFS was first described in the early twentieth century) [***147:*** *Bayrak O, et al. Pubovaginal sling materials and their outcomes. Turk J Urol. 2014 Dec; 40(4): 233–239;* ***148:*** *Goebell R. Zur operativen Beseitgung der angeborenen Incontinentia Vesicae. Dtsch Gynakol Urol. 1910;2:187–91*].

Ultimately, the surgeon needs to practice soundly, safely, ethically, and physiologically, in order to achieve the most optimal results for their patients.

As previously mentioned, all surgeries have potential complications. There are not any "risk-free" surgeries. This applies to SUI surgery. We have come a long way in effectively and safely treating women with SUI, with the use of mesh by following scientific principles and the Integral theory, as it applies to the continence mechanism of the urethra. If we do away with mesh then we do away with all utility and efficacy that has been established, and are back to problems with safety and efficacy of xenografts, allografts and other materials. Without building upon new paradigms, there are no randomized controlled trials, no meta-analysis, no Cochrane reviews, no science; thus no progress**.** The discovery of the TVT fits Kuhn's concept of a "scientific revolution," where changes in science emerge by revolution, not evolution. The midurethral sling is based upon reinforcing the pubourethral ligament, which has become the gold standard, and is already in the category of Kuhn's "normal science" concept [***149:*** *Kuhn, T. The structure of scientific revolutions. University of Chicago Press, Chicago, 3rd edn, pp 1-210*].

As noted previously, all surgeries have a potential for risks and complications. All surgery is potentially dangerous and requires due care. This is the expectation for all surgeons, whether it be pelvic or general or any other type of surgeon. It is the standard of care.

Due diligence is taught in residency, with the expectation that training is not complete once a residency program has been finished. Further training is essential, as new procedures, innovations, research, or a better way of performing an "old" procedure, develops over time. No matter the level, stage, or seniority of the surgeon, it is prudent to practice in a careful, attentive, cautious and humble fashion, so that the safety of the patient is kept at the forefront.

The steps that are to be undertaken in achieving this, is in following proper instruction via mentors, proctors, surgeon colleagues, device representatives, professional educational courses & videos, written literature; as well as seeking help in cases where there is uncertainty in the surgeon's hands. As with any surgery, proper patient selection, proper procedure and the proper performing surgeon is essential.

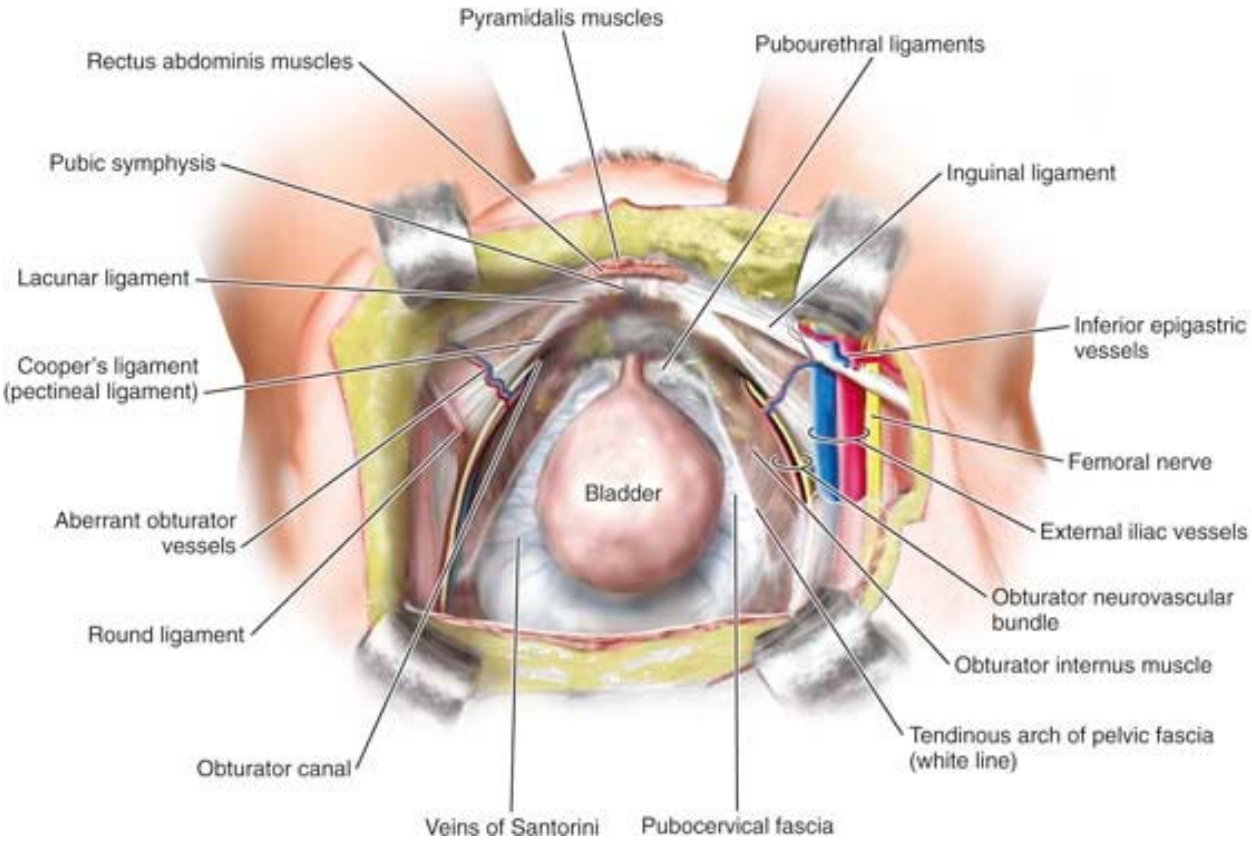
Specific surgical principles in the TVT MUS include:

- the use of cystoscopy
- proper plane development with full thickness vaginal mucosal flaps
- proper placement of the MUS– at the level of the mid-urethra, approximately 1-2 cm inferior to the urethral meatus
- deviation of the bladder to the contralateral side that the trocar is being placed
- laying of the small tape flat (without folding or bunching)
- placement in a “tension free manner”
- proper pre & post-op counseling, as well as follow-up

When taking on a new pelvic surgical procedure into one’s armamentarium, it is important to do the following:

- Know the fundamental risks of vaginal and UI surgery. However, particularly for a new procedure to the surgeon, it is expected that the surgeon learn and know all potential complications and recurrences. In addition, it is useful to know how to manage the treatment of complications and/or recurrences (or at least know who to refer a patient to or which expert is available to assist, should these occur). Mesh exposure, although relatively unique to mesh surgeries, should typically be managed by the original surgeon, as most are minor and easily treatable complications. However, in a more severe mesh complication, which is rare, appropriate referral should be made. The original surgeon, if possible, should continue to be involved the patient’s care.

- Pelvic anatomy is fundamental, but yet critical to the practice of pelvic surgeons. A surgeon should assess trocars and understand the organs, vessels, and nerves that are in the vicinity of the surgical procedure, which have the potential for injury.



 Having a basic understanding of the mesh properties is also valuable, such that mesh exposure can occur, as a result of a fibroblast reaction. Understanding the desired qualities of a mesh and why each quality is optimal is also important, such as the porosity, weight and absorbability.

 Literature searches and reviews can be of significant help.

 Prior experience with pelvic surgery, UI surgery and mesh surgery, can also influence the rate of adoption of the surgical procedure. Identifying one's limitations, resources and capabilities are factors that should be considered.

 Assessing FDA recommendations and how these apply to the procedures being performed by the surgeon. In the FDA alerts of 2008, 2011 and 2013 [***150:*** *FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence, 2008;* ***151****:Update on serious complications associated with transvaginal placement of surgical mesh for pelvic organ prolapse: FDA safety communication, July 2011;* ***152****: Considerations about surgical mesh, FDA March 2013*].

 FDA did not recommend that the MUS be removed from the market for the treatment of SUI, but that pelvic floor surgeons understand how to properly perform the

procedures, along with reporting complications and providing proper informed consent to their patients. It is considered the standard of care to be aware of these FDA alerts and updates.

- Reading the surgeon's monograph is an excellent source for learning & referring back to the TVT, in terms of preparation, anesthesia, abdominal/ suprapubic/vaginal incisions, bladder positioning, detailed written and illustrative description in the placement of the TVT device, as well as cystoscopic findings (including bladder perforation and subsequent readjustment of the TVT), antibiotic use, postop care, precautions, adverse reactions, contraindications, complications with its causes and recommendations for managing them.

- The IFU or instructions for use, is another resource.

- Of course, professional educational seminars & conferences, cadaveric and/or hands-on training, lectures are other important sources; all of which could also serve as CME (continuing medical education) credits. This is required for maintenance of board certification, as well.

III. The IFU and Professional Education

The Instructions for Use (IFU) provided with the Ethicon TVT Device is adequate in the warnings and instructions it provides. [*ETH.MESH.02340504-567; ETH.MESH.05225354-385.*] It notes that failure to properly follow the instructions may result in improper functioning of the device and lead to injury. It lists and explains the indications and contraindications for the device, providing detailed instructions for implanting the device. In addition, it notes that the device "should be used only by physicians trained in the surgical treatment of Stress Urinary Incontinence and specifically in implanting the "Gynecare TVT Device." It discusses possible adverse reactions, including punctures or lacerations of vessels, nerves, bladder and/or bowel, which may require surgical repair. It indicates that extrusion, erosion, fistula formation, inflammation and infection may occur, as well as lower urinary tract obstruction. Surgeons do not need an IFU in order to discuss all possible risks associated with the procedure, as surgeons already have basic fundamental medical knowledge about those risks from their education and training. Nor does the IFU need to advise surgeons that pain or other complications could be of a certain severity or duration, as all surgeons know that complications can be mild, moderate, or severe, or temporary or permanent.

The professional education I received, which included written materials, in didactic lecture and in training courses, provided by well-trained surgeons and knowledgeable Ethicon staff, was good and helpful. It included a discussion of complications and complication management (also mentioned in the surgeon's monograph).

For all of the reasons stated above, I believe the TVT device is safe, effective, and has a positive benefit-to-risk profile.

2/29/16
DATE

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